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I, LEANNE MYNOTT, MANAGER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003907107 for a patent by PROGEN INDUSTRIES LIMITED as filed on 23 December 2003.

WITNESS my hand this
Twelfth day of January 2005

LEANNE MYNOTT
MANAGER EXAMINATION SUPPORT
AND SALES

AUSTRALIA
Patents Act 1990

PROVISIONAL SPECIFICATION

Invention Title: Glycosaminoglycan (GAG) Mimetics

Applicant: Progen Industries Limited

The invention is described in the following statement.

TECHNICAL FIELD

The invention that is the subject of this application lies in the area of compounds that mimic the structure of certain carbohydrates. More particularly, the invention lies in the area of glycosaminoglycan (GAG) mimetics.

Specifically, the invention relates to compounds comprising at least one charged group that are designed to mimic the structure of GAGs. The invention also relates to methods for the preparation of the compounds, compositions comprising the compounds, and use of the compounds and compositions thereof for the anti-angiogenic, anti-metastatic, anti-inflammatory, anticoagulant and/or antithrombotic, antiviral and/or antibacterial treatment of a mammalian subject. The invention further relates to the use of the compounds and compositions thereof in the treatment of a mammalian subject having a condition amenable to treatment with such agents.

BACKGROUND ART

Glycosaminoglycans (GAGs) are linear, polyanionic polysaccharides that are produced by most animal cells and are usually found attached to a protein core [1,2]. GAGs occur abundantly (as proteoglycans) and are extruded by cells to the cell surface and into the extracellular matrix (ECM) [3]. It has been recognised that GAGs, especially those belonging to the heparan sulfate family (HS-GAGs), mediate numerous physiological processes. For example, HS-GAGs play key roles in cell growth and development, angiogenesis, coagulation, tumour metastasis, cell adhesion, activation of growth factors, binding of cytokines and chemokines, and infection by bacteria and viruses [4-6]. In recent years there has been a dramatic increase in the list of proteins that interact with GAGs and the list continues to grow. The emerging view is that unique sequences of extracellular GAGs bind specifically to important proteins and by doing so influence fundamental biological processes.

It has been shown that molecules that mimic the structure of certain GAGs (termed GAG mimetics) can bind to GAG-binding proteins and modulate their biological activity, e.g., the activation of AT-III by various pentasaccharides [7,8], or the activation of fibroblast growth factors (FGFs) by sucrose octasulfate [9]. Similarly, it has been shown that GAG mimetics can antagonise the binding of a GAG to its target protein and in so doing inhibit that protein's biological or disease function. For example, anti-cancer agents that have been developed to target HS-binding angiogenic growth factors include polysulfonated compounds [10], suramin and the related suradistas [11], and sulfated oligosaccharides [12,13].

It is an object of the present invention to find novel, small molecule GAG mimetics that bind strongly to GAG-binding proteins and modulate the function of such proteins. The compounds incorporate at least one negatively charged group to mimic the naturally occurring GAG monosaccharide unit(s) and to interact with the positively charged GAG- binding site of the target proteins, and may contain other substituents to mimic non-charged interactions around the above mentioned charged binding site. Since the synthesis of naturally occurring GAG fragments is tedious and difficult, synthetic approaches with easy manipulations and structural diversity were sought. The binding affinities of the GAG mimetics to a selection of GAG-binding, angiogenic growth factors was determined *via* a surface plasmon resonance (SPR) solution affinity assay.

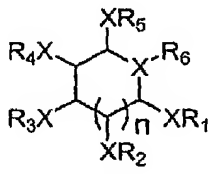
One aspect of the present invention is the utilisation of the Ugi reaction [14] to provide a diverse array of GAG mimetics. During the last decade, multicomponent reactions such as the Ugi reaction have attracted much attention in drug discovery and lead optimization [15], including the glycomics area [16] because of their synthetic potential for the generation of molecular diversity and applications in combinatorial chemistry. The capacity for variation in the manner in which the individual charged structures are connected to one another or to other functional groups as well as the scope of application to mimic the diverse structural variation of GAGs is demonstrated.

SUMMARY OF THE INVENTION

It is an object of the invention to provide novel charged compounds that have utility as GAG mimetics.

It is a further object of the invention to provide effective synthetic routes for the preparation of the subject compounds.

According to a first embodiment of the invention, there is provided a compound of the formula



I

wherein:

n is an interger having a value of 0,1 or 2;

X is independently chosen from C, C(O), N, N(O), O, S, S(O), $S(O)_2$, P, P(O), $P(O)_2$, Si, Si(O), $Si(O)_2$ or is absent; and

each of R_{1-6} is independently chosen from:

hydrogen;

halogen;

straight chain, cyclic, branched, substituted, heterocyclic, heteroatom substituted or non-substituted alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

straight chain, cyclic, branched, substituted, heterocyclic, heteroatom substituted or non-substituted alkyl, alkenyl, alkynyl, aryl, or heteroaryl acyl, bridged in an anhydro fashion;

phosphoryl groups such as phosphate, thiophosphate $-O-P(S)(OH)_2$; phosphate esters $-O-P(O)(OR)_2$; thiophosphate esters $-O-P(S)(OR)_2$; phosphonate $-O-P(O)OHR$; thiophosphonate $-O-P(S)OHR$; substituted phosphonate $-O-P(O)OR_1R_2$; substituted thiophosphonate $-O-P(S)OR_1R_2$; -O-P(S)(OH)(SH); and cyclic phosphate;

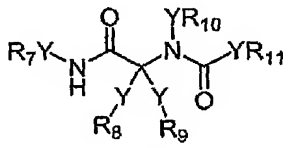
other phosphorus containing compounds such as phosphoramidite $-O-P(OR)-NR_1R_2$; and phosphoramidate $-O-P(O)(OR)-NR_1R_2$;

sulphur groups such as –O-S(O)(OH), -SH, -SR, -S(→ O)-R, $S(O)_2R$, $RO-S(O)_2^-$, $-O-SO_2NH_2$, $-O-SO_2R_1R_2$ or sulphamide $-NHSO_2NH_2$;

amino groups such as –NHR, $-NR_1R_2$, -NHAc, -NHCOR, -NH-O-COR, $-NHSO_3$, $-NHSO_2R$, $-N(SO_2R)_2$, and/or amidino groups such as $-NH-C(=NH)NH_2$ and/or ureido groups such as $-NH-CO-NR_1R_2$ or thiouriedo groups such as $-H-C(S)-NH_2$;

another unit of the structure **I**, attached through any position, wherein each of X and R_{1-5} are independently as defined above; or

a substructure based upon a group of the following formula:



II

wherein:

Y is

straight chain, cyclic, branched, substituted, heterocyclic, heteroatom substituted or non-substituted alkyl;

straight chain, cyclic, branched, substituted, heterocyclic, heteroatom substituted or non-substituted acyl;

aryl, substituted aryl, heteroaryl;

or absent; and

each of R_{7-11} is independently at least one structure according to formula **I**, as defined above for R_{1-6}, or a structure according to formula **II**.

According to a second embodiment of the invention, there is provided a pharmaceutical or veterinary composition for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation and/or coagulation/thrombosis, which composition comprises at least one compound according to the first embodiment together with a pharmaceutically or veterinarially acceptable carrier or diluent for said at least one compound.

A third embodiment of the invention comprises the use of a compound according to the first embodiment in the manufacture of a medicament for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation and/or coagulation/thrombosis.

According to a fourth embodiment of the invention there is provided a method for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation and/or coagulation/thrombosis, which method comprises administering to the subject an effective amount of at least one compound according to the first embodiment, or a composition comprising said at least one compound.

In the compound of formula I of the first embodiment defined above, the core structure is typically a pentose, hexose or heptose having either a D- or L- configuration.

With further regard to the compounds of the first embodiment, if not otherwise specified, alkyl, aryl and other substituent groups are used in accordance with their usual meaning in the art. For example, alkyl and aryl groups would normally have from 1 to 10 carbon atoms.

In order that the invention may be more readily understood and put into practice, one or more preferred embodiments thereof will now be described, by way of example only, with reference to the accompanying Tables.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The following abbreviations are used herein:

aFGF acidic fibroblast growth factor (or FGF-1)

bFGF	basic fibroblast growth factor (or FGF-2)
FGF	fibroblast growth factor
GAG	glycosaminoglycan
HS	heparan sulfate
SPR	surface plasmon resonance
VEGF	vascular endothelial growth factor

The present inventors have found that a broad range of compounds with GAG mimetic properties can be synthesised using a number of different strategies as demonstrated by the examples. These compounds have utility in the prevention or treatment in mammalian subjects of a disorder resulting from angiogenesis, metastasis, inflammation, microbial infections, coagulation or thrombosis. This utility results from the ability of the compounds to modulate the activity of GAG-binding proteins responsible for disease processes.

The GAG mimetics of the invention, as indicated above, can be synthesised using a number of different routes, including the Ugi reaction, and generally incorporating sulfonation in the process.

Preferred compounds according to the first embodiment of the invention as defined above include those depicted in generic structures I and II and those embraced by the Tables 1-4.

As indicated above, these compounds according to the invention have utility in the prevention or treatment in mammalian subjects of a disorder resulting from angiogenesis, metastasis, inflammation, microbial infection, coagulation or thrombosis. The compounds have particular utility in the treatment of the foregoing disorders in humans. The compounds are typically administered as a component of a pharmaceutical composition as described in the following paragraphs.

Pharmaceutical compositions for oral administration can be in tablet, capsule, powder or liquid form. A tablet can include a solid carrier such as gelatine or an adjuvant or an inert diluent. Liquid pharmaceutical compositions generally include a liquid carrier such as water, petroleum, animal or vegetable oils, a mineral oil or a synthetic oil. Physiological saline solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included. Such compositions and preparations will generally contain at least 0.1 wt% of the compound.

Parenteral administration includes administration by the following routes: intravenously, cutaneously or subcutaneously, nasally, intramuscularly, intraocularly,

transepithelially, intraperitoneally and topically. Topical administration includes dermal, ocular, rectal, nasal, as well as administration by inhalation or by aerosol means. For intravenous, cutaneous or subcutaneous injection, or injection at a site where treatment is desired, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of skill in the art will be well able to prepare suitable solutions using, for example, solutions of the subject compounds or derivatives thereof.

In addition to the at least one compound and a carrier or diluent, compositions according to the invention can further include a pharmaceutically or veterinarially acceptable excipient, buffer, stabiliser, isotonicising agent, preservative or anti-oxidant or any other material known to those of skill in the art. It will be appreciated by the person of skill that such materials should be non-toxic and should not interfere with the efficacy of the compound(s). The precise nature of any additive may depend on the route of administration of the composition; that is, whether the composition is to be administered orally or parenterally. With regard to buffers, aqueous compositions typically include such substances so as to maintain the composition at a close to physiological pH or at least within a range of about pH 5.0 to 8.0.

Compositions according to the invention can also include active ingredients in addition to the at least one compound. Such ingredients will be principally chosen for their efficacy as anti-angiogenic, anti-metastatic, anti-inflammatory, anti-coagulant, anti-thrombotic, anti-viral and/or anti-bacterial agents but can be chosen for their efficacy against any associated condition.

A pharmaceutical or veterinary composition according to the invention will be administered to a subject in either a prophylactically effective or a therapeutically effective amount as necessary for the particular situation under consideration. The actual amount of at least one compound administered by way of a composition, and rate and time-course of administration, will depend on the nature and severity of the condition being treated or the prophylaxis required. Prescription of treatment such as decisions on dosage and the like will be within the skill of the medical practitioner or veterinarian responsible for the care of the subject. Typically however, compositions for administration to a human subject will include between about 0.01 and 100 mg of the compound per kg of body weight and more preferably between about 0.1 and 10 mg/kg of body weight.

The compounds can be included in compositions as pharmaceutically or veterinarially acceptable derivatives thereof. As used herein "derivatives" of the compounds includes salts, coordination complexes with metal irons such as Mn^{2+} and Zn^{2+}, esters such as *in vivo* hydrolysable esters, free acids or bases, hydrates, or prodrugs. Compounds having acidic groups such as phosphates or sulfates can form salts with alkaline or alkaline earth metals such as Na, K, Mg and Ca, and with organic amines such as triethylamine and Tris (2-hydroxyethyl) amine. Salts can also be formed between compounds with basic groups, such as amines, with inorganic acids such as hydrochloric acid, phosphoric acid or sulfuric acid, or organic acids such as acetic acid, citric acid, benzoic acid, fumaric acid, or tartaric acid. Compounds having both acidic and basic groups can form internal salts.

Esters can be formed between hydroxyl or carboxylic acid groups present in the compound and an appropriate carboxylic acid or alcohol reaction partner, using techniques that will be well known to those of skill in the art.

Prodrug derivatives of the compounds of the invention can be transformed *in vivo* or *in vitro* into the parent compounds. Typically, at least one of the biological activities of a parent compound may be suppressed in the prodrug form of the compound, and can be activated by conversion of the prodrug to the parent compound or a metabolite thereof. Examples of prodrugs are glycolipid derivatives in which one or more lipid moieties are provided as substituents on the moieties, leading to the release of the free form of the compound by cleavage with an enzyme having phospholipase activity. Prodrugs of compounds of the invention include the use of protecting groups which may be removed *in vivo* to release the active compound or serve to inhibit clearance of the drug. Suitable protecting groups will be known to those of skill in the art and include an acetate group.

As also indicated above, compounds according to the invention have utility in the manufacture of a medicament for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation/thrombosis and/or microbial infection. Processes for the manufacture of such medicaments will be known to those of skill in the art and include the processes used to manufacture the pharmaceutical compositions described above.

The compounds falling within the scope of the invention have been found to have bind growth factors. In particular, it has been established that the compounds have affinity for aFGF, bFGF and VEGF The compounds thus have utility as anti-angiogenic, anti-metastatic and/or anti-inflammatory agents in the treatment of mammalian subjects including humans.

The uses of the compounds include the treatment of angiogenesis-dependent diseases such as angiogenesis associated with the growth of solid tumours, proliferative retinopathies and rheumatoid arthritis, as well as the treatment of inflammatory diseases and conditions. The compounds may also activate the growth factors and could thus be used in cardiovascular treatments.

As further indicated above, the compounds of the invention additionally have utility as anti-coagulant or anti-thrombotic agents. The compounds can therefore be used for both the prophylaxis and treatment of many thrombotic and cardiovascular diseases, the most notable of these being deep venous thrombosis, pulmonary embolism, thrombotic stroke, peripheral arterial thrombosis, unstable angina and myocardial infarction. Since compositions of the charged aminoacid compounds can be delivered orally, the compounds are an attractive alternative to warfarin, a widely used oral anticoagulant with severe side effects.

Having broadly described the invention, non-limiting examples of the compounds, their synthesis, and their biological activities, will now be given with reference to the accompanying Tables which will be briefly described in the following section of this specification.

General Procedures

General procedure for alkylation and deprotection of diols

The diol (1 eq.) in DMF was added dropwise to a cooled (0°), stirred suspension of pre-washed (hexane) NaH (5 eq.) in DMF. Once the addition was complete, stirring was maintained (0°→ r.t., 20 min). The mixture was cooled (0°, 5 min) and the alkyl halide (2 eq.) was introduced dropwise with continued stirring (0°→ r.t., o/n). The mixture was cooled once again (0°) and MeOH (5 mL) was introduced with continued stirring (5 min). The solvent was evaporated and the residue subjected to workup (EtOAc) and flash chromatography to homogeneity (TLC). This residue was co-evaporated (2 × 10 mL MeCN). The crude mixture and *p*-TsOH·H_2O (50 mg) in MeOH/MeCN (1:1) was heated under reflux (1 h). The mixture was cooled (r.t.) and Et_3N (100 µL) was added prior to evaporation of the solvent. The residue was subjected to flash chromatography (EtOAc/hexane) to yield the diol.

General procedure for sulfonation of alcohols

A mixture of the alcohol and SO_3·trimethylamine (2 eq per hydroxyl group) in DMF was heated (60°, o/n). The cooled (r.t.) reaction mixture was treated with MeOH and then made basic (to pH>10) by the addition of Na_2CO_3 (10% w/w). The mixture was filtered and the filtrate evaporated and co-evaporated (H_2O). Where deacylation of the sulfated product was required, the crude product was taken up in water and 1M NaOH was added (2 eq per acyl

group). When deprotection was complete the product was carried through to the next stage. The crude sulfated material in H_2O was subjected to size exclusion chromatography. The pure fractions were evaporated and co-evaporated (H_2O) and then lyophilised (H_2O) to yield the sulfated product. When required, after lyophilisation the product was passed through an ion-exchange resin column (AG®-50W-X8, Na^+ form, 1×4 cm, deionized H_2O, 15 mL) in order to transfer the product uniformly into the sodium salt form. The solution collected was evaporated and lyophilised to give the final product as a colourless glass or white power.

Size exclusion chromatography

Size exclusion chromatography (SEC) was performed over Bio-Gel P-2 in a 5 × 100 cm column with a flow rate of 2.8 mL/min of 0.1 M NH_4HCO_3, collecting 2.8 min (7.8 mL) fractions. Fractions were analysed for carbohydrate content by TLC (charring) and/or for poly-charged species by the dimethyl methylene blue test, and then for purity by capillary electrophoresis (CE) and those deemed to be free of salt were pooled and lyophilised.

In the cases of the presence of undersulfated by-products or other salt contaminants (normally only small amounts, but often detected), an LH20 SEC step (2 × 95 cm, deionized water, 1.2 mL/min, 3.5 min per vial) was applied to remove them completely.

Dimethyl methylene blue Test

Dimethyl methylene blue (DMB) reagent was prepared by dissolving 16 mg of DMB in 1 L of deionized water containing 3.04 g of glycine, 2.37 g of NaCl. 0.1 M HCl (95 ml) was added to adjust the pH to 3.0. The stock solution was stored in a brown coloured bottle at r.t. (the solution was stable for at least 3 months under such conditions).

A 96-well microtitre plate was loaded with 10 µL of fraction solution per well. 55 µL of DMB stock solution was added into each used well. An instant colour change from blue to pink indicated the presence of polycharged species, i.e., sulfated product fractions.

General procedure for NIS glycosylations

Glycosyl acceptor (1 eq), thioglycoside donor (1.1 eq), 500 mg of freshly activated powdered 3Å molecular sieves and 10 mL of dry DCM were stirred at -20° for 20 min before 1.3 eq of NIS and 1 drop of TfOH were added. Stirring was continued at -20° until the reaction was complete by TLC (~1 h) before 400 µL of Et_3N was added. Evaporation (*in vacuo*) onto silica gel and flash chromatography yielded the glycosylated product.

General procedure for Ugi four-component reaction

Solutions of the acid (1 eq), amine (1 eq), carbonyl compound (1 eq) and isocyanide (1 eq) in MeOH, MeOH-THF (varied ratios) or $CHCl_3$ were transferred into a reaction vial (final

concentration: 0.1-0.5 M). When D-glucuronic acid was the acid component, it was added as a solid. In the case of bis-acid, bis-amine, bis-aldehyde or bis-isocyanide, the amount was 0.5 eq. The mixture was stirred or shaken at r.t. or 60 °C for 1 h to 5 days. The progress of the reaction was monitored by TLC. The mixture was evaporated and the residue was purified by flash chromatography or dried completely under high vacuum followed by direct peracetylation and purification by flash chromatography.

General procedure for acetylation of hydroxyl groups:

The corresponding alcohol was dissolved in DCM-pyridine (15:1 v/v, 0.15 M) containing DMAP (0.42 mol%). Acetic anhydride (2 eq per hydroxyl) was added and the mixture was stirred at r.t. o/n. The mixture was poured into ice-chilled 0.5 M HCl and extracted with $CHCl_3$. The organic phase was separated and washed with cold 0.5 M HCl (×2), brine, and dried ($MgSO_4$). The solution was filtered and evaporated. The residue was purified by flash chromatography (gradient elution with hexane-EtOAc) to give pure product.

General procedure for Zemplén deacetylation/debenzoylation:

A solution of the acetate/benzoate in anhydrous MeOH (0.1 M) was treated with a solution of sodium methoxide in MeOH (1.35 M, 0.2-0.6 eq). The mixture was stirred at r.t. for 1-3 h (monitored by TLC). Acidic resin AG®-50W-X8 (H^+ form) was added to adjust the pH to 6-7, the mixture was filtered and the resin was rinsed with MeOH. The combined filtrate and washings were evaporated *in vacuo* and thoroughly dried to give the poly-ol product.

General procedure for deprotection of benzyl ethers via hydrogenolysis

To a solution of the benzyl ether-protected compound (0.03 mmol) in MeOH or EtOH (2 mL) was added 5% Pd/C or 20% $Pd(OH)_2$ on charcoal (30 mg or excess). The mixture was loaded in a miniclave (Büchi AG, Uster/Switzerland) and stirred under hydrogen atmosphere (50 psi) for 2-10 h. Alternatively, the mixture was bubbled with hydrogen gas for 1 h then stirred at r.t. under 1 atmosphere of hydrogen for 1-5 days. The reaction was monitored by TLC (EtOAc or MeCN-water 10:1). The mixture was filtered and rinsed with MeOH, or EtOH. The filtrate was evaporated and dried under high vacuum, checked by ^1H NMR, freeze-dried and used directly for sulfonation.

Methylation of hydroxyl groups

The dried poly-ol was dissolved in anhydrous DMF (0.04 M) under argon and stirred with NaH (60% suspension in mineral oil, 1.2 eq per hydroxyl) at r.t. for 1 h. Iodomethane (1.2 eq per hydroxyl) was added and stirring continued o/n. MeOH was added and the mixture was evaporated onto silica and purified by flash chromatography.

Example 1: PG2038

Step a: Methyl 3,4,6-tri-O-acetyl-2-O-benzyl-α-D-galactopyranosyl-(1→ 4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside.

Methyl 2,3,6-tri-O-benzyl-β-D-glucopyranoside [17] (150 mg, 322 μmol), *methyl 3,4,6-tri-O-acetyl-2-O-benzyl-1-thio*-β-D-*galactopyranoside* [18] (151 mg, 354 μmol) and 200 mg of 3Å molecular sieves were subjected to the general NIS glycosylation procedure using 95 mg (422 μmol) of NIS. Flash chromatography (gradient elution 20:80 to 25:75 EtOAc:hexanes) yielded 274 mg of partially deacetylated material. To this mixture was added 10 mL of DCM, 200 μL of acetic anhydride, 200 of μL Et_3N and 2 mg of DMAP, and the solution was stirred for 1 h before evaporation and flash chromatography (gradient elution 25:75 to 30:70 EtOAc:hexanes) to give 180 mg (66%) of the title compound as a colourless glass. ^{1}H n.m.r. (400 MHz, $CDCl_3$) δ: 7.05-7.35 (m, 20H, 4×Ph), 5.74 (d, 1H, $J_{1,2}$ = 4.0, H1^{II}), 5.29 (dd, 1H, $J_{3,4}$ = 3.2, $J_{4,5}$ = 1.2, H4^{II}), 5.23 (dd, 1H, $J_{2,3}$ = 10.8, H3^{II}), 4.92 (d, 1H, J_{gem} = 12.0, $PhCH_2$), 4.85 (d, 1H, J_{gem} = 10.8, $PhCH_2$), 4.55-4.69 (m, 4H, $PhCH_2$), 4.42 (AB, 1H, J_{gem} = 12.0, $PhCH_2$), 4.40 (AB, 1H, $PhCH_2$), 4.32 (d, 1H, $J_{1,2}$ = 7.6, H1^I), 4.10 (dt, 1H, $J_{5,6}$ = 6.8, H5^{II}), 3.88-3.96 (m, H, H5^I+H6^I), 3.82 (dd, 1H, J_{gem} = 11.1, H6^{II}), 3.70-3.76 (m, 4H, H2×H6^I+H2^{II}+H3^I), 3.56 (s, 3H, OMe), 3.5-3.6 (m, 1H, H4^I), 3.45 (dd, 1H, $J_{2,3}$ = 9.0, H2^I), 2.02 (s, 3H, Ac), 1.93 (s, 3H, Ac), 1.88 (s, 3H, Ac). ^{13}C n.m.r. (100 MHz, $CDCl_3$) δ: 170.17, 170.06, 169.87, 138.82, 138.20, 138.13, 137.68, 128.33, 128.25, 128.19, 128.04, 127.61, 127.57, 127.49, 127.46, 127.01, 126.39, 104.42, 97.12, 84.49, 82.26, 74.46, 74.27, 73.69, 73.31, 73.28, 73.02, 69.47, 69.17, 68.35, 66.60, 61.62, 56.96, 20.69, 20.63, 20.58.

Step b: Methyl 3,4,6-tri-O-acetyl-α-D-galactopyranosyl-(1→ 4)-β-D-glucopyranoside.

Pearlman's catalyst (20 mg) and 20 μL of acetic acid were added to a solution of 90 mg (106 μmol) of *methyl 3,4,6-tri-O-acetyl-2-O-benzyl-α-D-galactopyranosyl-(1→ 4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside* in 10 mL of MeOH. An atmosphere of hydrogen was applied with 3 vacuum purges and the suspension was stirred for 3 days. After filtration, evaporation and co-evaporation with PhMe the residue was subjected to flash chromatography (gradient elution 100:0 to 100:3 EtOAc:MeH) to yield 47 mg (91%) of the title compound. ^{1}H n.m.r. (400 MHz, CD_3OD) δ: 5.39 (br d, 1H, $J_{3,4}$ = 3.0, H4^{II}), 5.32 (d, 1H, $J_{1,2}$ = 3.8, H1^{II}), 5.10 (dd, 1H, $J_{2,3}$ = 10.6, H3^{II}), 4.38 (br t, 1H, $J_{5,6}$ = 6.8, H5^{II}), 4.20 (d, 1H, $J_{1,2}$ = 7.8, H1^I), 4.09 (app d (ABX), 2H, $J_{5,6}$ = 6.5, H6^{II}), 4.00 (dd, 1H, H2^{II}), 3.92 (dd, 1H, $J_{5,6A}$ = 1.7, J_{gem} = 12.2, H6A^I), 3.80 (dd, 1H, $J_{5,6B}$ = 4.8, H6B^I), 3.62 (dis t, 1H, $J_{2,3-3,4}$ = 9.1, H3^I), 3.56 (part obs t, 1H, $J_{3,4-4,5}$ =

9.3, $H4^I$), 3.53 (s, 3H, OMe), 3.42 (ddd, 1H, $J_{4,5}$ = 9.4, $H5^I$), 3.22 (dd, 1H, $J_{2,3}$ = 9.1, $H2^I$), 2.10 (s, 3H, AcO), 2.05 (s, 3H, AcO), 2.00 (s, 3H, AcO).

Step c: Methyl 2-O-sulfo-α-D-galactopyranosyl-(1→ 4)-2,3,6-tri-O-sulfo-β-D-glucopyranoside, tetrasodium salt (PG2038)

The above disaccharide (32.2 mg, 0.667 mmol), was subjected to the standard sulfonation and deacetylation procedures to give the title compound as a white foam (4.0 mg, 7.8%, 96% purity, CE: 7.18 min). ^{1}H NMR (D_2O, 400 MHz): 5.473 (d, 1H, $J_{II\text{-}2II}$ = 3.6, $H1^{II}$), 4.833 (d, 1H, $J_{II\text{-}2I}$ = 2.8, $H1^I$), 4.60 (overlapped with water, 1H, $H3^I$), 4.551 (m, 1H, $H2^I$), 4.306 (dd, 1H, $J_{2II\text{-}3II}$ = 10.2, $H2^{II}$), 4.17-4.06 (m, 4H, $H4^I$, $H5^I$ and $H6^I$), 3.902 (d, 1H, $J_{3II\text{-}4II}$ = 3.6, $H4^{II}$), 3.867 (dd, 1H, $H3^{II}$), 3.616 (dd, 1H, $J_{6axII\text{-}6eqII}$ = 12.0, $J_{5II\text{-}6axII}$ = 7.2, $H6ax^{II}$), 3.564 (dd, 1H, $J_{5II\text{-}6eqII}$ = 5.2, $H6eq^{II}$), 3.363 (dd, 1H, $H5^{II}$), 3.343 (s, 3H, CH_3O).

Example 2: PG2046 and PG2047

Step a: 2-Azido-3,4,6-tri-O-benzoyl-2-deoxy-α-D-glucopyranosyl-(1→ 4)-1,6-anhydro-2-azido-2-deoxy-3-O-benzyl-β-D-glucopyranose

A solution of *3,4,6-tri-O-acetyl-2-azido-2-deoxy-D-glucopyranosyl trichloro-acetimidate* [19] (201 mg, 0.453 mmol) and *1,6-anhydro-2-azido-3-O-benzyl-2-deoxy-β-D-glucopyranose* [20] (84 mg, 0.302 mmol) in 1,2-DCE (5 mL) was stirred in the presence of activated mol. sieves (300 mg of 3Å powder) under an atmosphere of argon (r.t., 30 min). The mixture was cooled (–20°) with continued stirring (10 min) and TBDMSOTf (21 μL, 0.091 mmol) was introduced drop-wise and stirring maintained (–20°, 10 min). Et_3N (100 μL) was introduced and the mixture filtered and evaporated. The residue was subjected to aqueous workup (EtOAc) and flash chromatography (10-40% EtOAc/hexanes) to yield a pale yellow coloured oil (130 mg). This residue was co-evaporated (2 × 10 mL MeCN) then subjected to the Zemplén deacetylation general procedure. The product was subjected to aqueous workup (EtOAc) to yield a colourless oil (98 mg). This residue was co-evaporated (2 × 10 mL MeCN). BzCl (210 μL, 1.81 mmol) was added to a solution of the crude product (0.302 mmol, max.) and pyridine (2 mL) in 1,2-DCE (3 mL) and the combined mixture stirred (r.t., o/n). The mixture was cooled (0°) and MeOH (2 mL) was introduced with continued stirring (0°→ r.t., 2 min) before evaporation and co-evaporation (toluene) of the solvent. The residue was subjected to aqueous workup (EtOAc) and flash chromatography (10-30% EtOAc/hexanes) to yield two compounds.

Firstly, the title compound as a colourless foam (101 mg, 46%, 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (s, 1 H; H-2^I), 3.41 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 10.7 Hz; H-6^I), 3.61 (s, 1 H; H-

3^{I}), 3.39 (s, 1 H; H-4^{I}), 4.05 (d, 1 H, $J_{6,6}$ 7.3 Hz; H-6^{I}), 4.41-4.49 (m, 2 H; H-6^{II}), 4.55, 4.68 (AB quartet, $J_{A,B}$ 11.9 Hz; CH_2Ph), 4.79 (ddd, 1 H, $J_{4,5}$ 10.3, $J_{5,6}$ 2.9, 5.9 Hz; H-5^{II}), 4.91 (br d, 1 H, $J_{5,6}$ 5.5 Hz; H-5^{I}), 5.08 (d, 1 H, $J_{1,2}$ 3.6 Hz; H-1^{II}), 5.51 (dd, 1 H, $J_{3,4}$ 9.5, $J_{4,5}$ 10.2 Hz, H-4^{II}), 5.60 (s, 1 H,; H-1^{I}), 6.10 (dd, 1 H, $J_{2,3}$ 10.7, $J_{3,4}$ 9.3 Hz; H-3^{II}), 7.29-7.55, 7.89-8.03 (2 m, 20 H; ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.74, 61.47, 63.30, 64.84, 69.19, 69.49, 70.52, 73.17, 74.62, 78.12, 79.57 (11 C; C-2^{I}-6^{I}, $C2^{II}$-6^{II}, CH_2Ph), 100.71, 101.16 (2 C; C-1^{I}, C-1^{II}), 128.10, 128.42, 128.57, 128.61, 128.64, 128.81, 128.88, 129.15, 129.86, 129.90, 130.06, 130.17, 133.43, 133.53, 133.74, 137.48 (Ar), 165.61, 165.62, 166.26 (3 C; C=O).

Next, *2-azido-3,4,6-tri-*O*-benzoyl-2-deoxy-β-*D*-glucopyranosyl-(1→ 4)-1,6-anhydro-2-azido-2-deoxy-3-*O*-benzyl-*β-D*-glucopyranose* as a colourless oil (27 mg, 12%, 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (s, 1 H; H-2^{I}), 3.74 (dd, 1 H, $J_{5,6}$ 6.2, $J_{6,6}$ 7.1 Hz; H-6^{I}), 3.79-3.88 (m, 2 H; H-2^{II}, H-3^{I}), 3.88 (ddd, $J_{4,5}$ 9.2, $J_{5,6}$ 3.1, 4.7 Hz; H-5^{II}), 3.95 (br s, 1 H; H-4^{I}), 4.10 (d, 1 H, $J_{6,6}$ 7.3 Hz; H-6^{I}), 4.34 (dd, 1 H; $J_{5,6}$ 4.9, $J_{6,6}$ 12.2 Hz; H-6^{II}), 4.50 (dd, 1 H, $J_{5,6}$ 3.1, $J_{6,6}$ 12.3 Hz, H-6^{II}), 4.52, 4.59 (AB quartet, $J_{A,B}$ 12.0 Hz; CH_2Ph), 4.65 (d, 1 H, $J_{1,2}$ 7.9 Hz; H-1^{II}), 4.69 (br d, 1 H, $J_{5,6}$ 5.5 Hz; H-5^{I}), 5.44 (t, 1 H, $J_{2,3=3,4}$ 9.7 Hz; H-3^{II}), 5.49 (br s, 1 H; H-1^{I}), 5.51 (t, 1 H, $J_{3,4=4,5}$ 9.6 Hz; H-4^{II}), 7.23-7.50, 7.84-7.96 (2 m, 20 H; ArH).

Step b: 2-Deoxy-2-sulfamido-α-D-glucopyranosyl-(1→ 4)-1,6-anhydro-2-deoxy-2-sulfamido-3-O-benzyl-β-D-glucopyranose, disodium salt (PG2046)

A mixture of *2-azido-3,4,6-tri-*O*-benzoyl-2-deoxy-α-D-glucopyranosyl-(1→ 4)-1,6-anhydro-2-azido-2-deoxy-3-*O*-benzyl-β-D-glucopyranoside* (127 µmol), Pearlman's catalyst (11 mg), and ammonium formate (300 mg) in 2:1 MeOH:EtOAc (7 mL) was heated to 65° under argon until complete by TLC. The mixture was cooled to r.t., filtered (0.2 µm) and evaporated. The crude amine was purified by SPE (300 mg C18 Waters cartridge, equilibrated with 5:95 MeOH:H_2O, gradient eluted 5:95 to 100:0 MeOH:H_2O) to yield 53 mg of the diamine (58%). Without further purification, to the diamine was added DMF (5 mL), SO_3•Me_3N (41 mg, 295 µmol) and $NaHCO_3$ (40 mg, 475 µmol). The mixture was heated to 60° for 1 h then cooled to rt and quenched with ice and Na_2CO_3 (sat. aqueous). This suspension was stored at -18° o/n and the sample was filtered. The filtrate was evaporated. Water (1 mL) and NaOH (250 µL, 1M) were added and the solution was stirred overnight then loaded directly onto the SEC column (general procedures) to yield 22 mg (28 % over three steps) of the title compound. ^{1}H NMR (400 MHz, D_2O, solvent suppressed) δ: 7.35-7.21 (m, 5H, ArH),

5.43 (br s, 1H, $H1^{I}$), 5.18 (d, 1H, $J_{1\text{-}2}$ = 3.6, $H1^{II}$), 4.72-4.69[1] (m, 1H, $H5^{I}$), 4.54-4.52[1] (m, 2H, $ArCH_2$), 4.05 (d, 1H, J_{gem} = 7.9, $H6A^{I}$), 3.85 (br s, 1H, $H3^{I}$), 3.76-3.58 (m, 5H), 3.51 (dd, 1H, $J_{2\text{-}3}$ = 10.4, $J_{3\text{-}4}$ = 9.1, $H3^{II}$), 3.34 (t, 1H, $J_{3\text{-}4\text{-}4\text{-}5}$ = 9.2, $H4^{II}$), 3.23 (br s, 1H, $H2^{I}$), 3.12 (dd, 1H, $H2^{II}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.3, 124.8, 124.6, 124.4, 96.9, 95.1, 72.7, 71.5, 70.8, 68.3, 68.2, 67.2, 66.0, 61.0, 56.6, 54.0, 49.8.

Step c: 2-Deoxy-2-sulfamido-α-D-glucopyranosyl-(1→ 4)-1,6-anhydro-2-deoxy-2-sulfamido-β-D-glucopyranoside, disodium salt (PG2047)

A mixture of *2-deoxy-2-sulfamido-α-D-glucopyranosyl-(1→ 4)-1,6-anhydro-2-deoxy-2-sulfamido-3-O-benzyl-β-D-glucopyranoside, disodium salt* (12.9 mg, 20.8 μmol) and Pearlman's catalyst (5 mg) in purified water (2 mL) was subjected to 50 psi H_2 overnight. The mixture was filtered and lyophilised to yield 10.7 mg (98 %) of the title compound. ^1H NMR (400 MHz, D_2O) δ: 5.47 (br s, 1H, $H1^{I}$), 5.20 (d, 1H, $J_{1\text{-}2}$ = 3.5, $H1^{II}$), 4.68 (br d, 1H, $J_{5\text{-}4}$ = 5.5, H5), 4.07 (d, 1H, J_{gem} = 7.6, $H6A^{I}$), 3.98 (br s, 1H, $H3^{I}$), 3.75-3.64 (m, 4H), 3.52 (t, 1H, $J_{2\text{-}3\text{-}3\text{-}4}$ = 9.3, $H3^{II}$), 3.34 (t, 1H, $J_{3\text{-}4\text{-}4\text{-}5}$ = 9.3, $H4^{II}$), 3.13 (obs. dd[2], 1H, $H2^{II}$), 3.11 (br s, 1H, $H2^{I}$).

Example 3: PG2039 and PG2037

Step a: Methyl 3,4-di-O-acetyl-2,6-di-O-benzyl-α-D-galactopyranosyl-(1→ 4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside

287 mg (618 μmol) of *methyl 2,3,6-tri-O-benzyl-β-D-glucopyranoside*, 302 mg (618 μmol) of *ethyl 3,4-di-O-acetyl-2,6-O-dibenzyl-1-thio-β-D-galactopyranoside* [21] and 700 mg of 3Å molecular sieves were subjected to the general NIS glycosylation procedure using 181 mg (803 μmol, 1.3eq) of NIS. Flash chromatography (2.5 × 20 cm, gradient elution 1:5 to 1:3 EtOAc:Hexanes) yielded the title compound as a colourless gum (176 mg, 32%). ^1H NMR (400 MHz, $CDCl_3$, 400 MHz): 7.40-7.12 (m, 25H, Ph), 5.818 (d, 1H, $J_{1II\text{-}2II}$ = 3.6, $H1^{II}$), 5.481 (d, 1H, $J_{4II\text{-}3II}$ = 3.2, $H4^{II}$), 5.309 (dd, 1H, $J_{3II\text{-}2II}$ = 10.8, $J_{3II\text{-}4II}$ = 3.2, $H3^{II}$), 4.980 (d, 1H, J_{gem} = 11.6, a-$PhCH_2$), 4.904 (d, 1H, J_{gem} = 11.2, b-$PhCH_2$), 4.748 (d, 1H, J_{gem} = 11.6, a-$PhCH_2$), 4.67-4.57 (m, 3H, b-$PhCH_2$ and c-$PhCH_2$), 4.479 (d, 1H, J_{gem} = 12.8, d-$PhCH_2$), 4.443 (d, 1H, J_{gem} = 12.8, d-$PhCH_2$), 4.415 (d, 1H, J_{gem} = 11.6, e-$PhCH_2$), 4.360 (d, 1H, $J_{1I\text{-}2I}$ = 8.0, $H1^{I}$), 4.201 (d, 1H, J_{gem} = 12.6, e-$PhCH_2$), 4.153 (t, 1H, $J_{5II\text{-}6axII}$ = 7.2, $J_{5II\text{-}6eqII}$ = 6.0, $H5^{II}$), 4.072 (t, 1H, $J_{4I\text{-}3I}$ = 9.0, $J_{4I\text{-}5I}$ = 9.0, $H4^{I}$), 3.858 (dd, 1H, $J_{2II\text{-}3II}$ = 10.8, $J_{2II\text{-}1II}$ = 3.6, $H2^{II}$), 3.82-3.76 (m, 3H, $H3^{I}$, $H6ax^{I}$ and H6 eq^{I}), 3.597 (s, 3H, OMe), 3.62-3.57 (m, 1H, $H5^{I}$), 3.507 (t, 1H, $J_{2I\text{-}3I}$ =

[1] Affected by the solvent suppression signal.
[2] Partially obscured by $H2^{I}$.

8.4, $J_{2I\text{-}1I}$ = 8.0, $H2^{I}$), 3.347 (dd, 1H, $J_{6eqII\text{-}6axII}$ = 9.2, $J_{6eqII\text{-}5II}$ = 6.0, $H6eq^{II}$), 3.291 (dd, 1H, $J_{6axII\text{-}6eqII}$ = 9.2, $J_{6axII\text{-}5II}$ = 7.2, $H6ax^{II}$), 1.958 (s, 3H, OAc), 1.930 (s, 3H, OAc). ^{13}C NMR (100 MHz, $CDCl_3$, 100 MHz): 169.94 (CO), 169.78 (CO), 138.88, 138.35, 138.24, 137.73 and 137.64 (5x *ipso*-Ph), 128.25, 128.22, 128.21, 128.15, 128.12, 128.00, 127.80, 127.57, 127.52, 127.46, 127.41, 127.37, 126.93, 126.37, 104.40, 97.16, 84.63, 82.31, 74.42, 74.30, 73.70, 73.25, 73.16, 73.14, 72.98, 69.73, 69.07, 68.89, 67.64, 67.50, 56.86, 20.71, 20.55.

Step b: Methyl 3,4-di-O-acetyl-α-D-galactopyranosyl-(1→ 4)-β-D-glucopyranoside.

Following the standard debenzylation procedure, *methyl 3,4-di-O-acetyl-2,6-di-O-benzyl-α-D-galactopyranosyl-(1→ 4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside* (88 mg, 98.8 µmol) was deprotected to give the title compound as a colourless powder (42 mg, 97%). ^{1}H NMR (D_2O, 400 MHz): 5.394 (d, 1H, $J_{1II\text{-}2II}$ = 3.6, $H1^{II}$), 5.294 (d, 1H, $J_{4II\text{-}3II}$ = 3.2, $H4^{II}$), 4.953 (dd, 1H, $J_{3II\text{-}2II}$ = 10.4, $J_{3II\text{-}4II}$ = 3.2, $H3^{II}$), 4.229 (d, 1H, $J_{1I\text{-}2I}$ = 8.4, $H1^{I}$), 4.080 (t, 1H, $J_{5II\text{-}6axII}$ = 6.4, $J_{5II\text{-}6eqII}$ = 6.0, $H5^{II}$), 3.965 (dd, 1H, $J_{2II\text{-}3II}$ = 10.4, $J_{2II\text{-}1II}$ = 3.6, $H2^{II}$), 3.803 (dd, 1H, $J_{6eqI\text{-}6eqI}$ = 12.0, $J_{6eqI\text{-}5I}$ = 1.6, $H6eq^{I}$), 3.67-3.59 (m, 2H, $H6ax^{I}$ and $H3^{I}$), 3.54-3.40 (m, 4H, $H4^{I}$, $H5^{I}$ and $H6^{II}$), 3.407 (s, 3H, OMe), 3.134 (dd, 1H, $J_{2I\text{-}3I}$ = 9.2, $J_{2I\text{-}1I}$ = 8.4, $H2^{I}$), 2.012 (s, 3H, OAc), 1.909 (s, 3H, OAc). ^{13}C NMR (D_2O, 100 MHz): 173.57, 173.47, 103.20, 99.71, 77.12, 76.30, 74.57, 73.09, 70.89, 69.94, 69.04, 66.45, 60.82, 60.18, 57.31, 20.34, 20.09.

Step c: Methyl 2,6-di-O-sulfo-α-D-galactopyranosyl-(1→ 4)-2,3,6-tri-O-sulfo-β-D-glucopyranoside, pentasodium salt (PG2039)

Following the standard sulfonation/deacetylation procedures, 42 mg (95.4 µmol) of *methyl 3,4-di-O-acetyl-α-D-galactopyranosyl-(1→ 4)-β-D-glucopyranoside* was converted to the title compound as a white powder (14.8 mg, 18%, CE: 6.12 min). ^{1}H NMR (D_2O, 400 MHz): 5.404 (d, 1H, $J_{1II\text{-}2II}$ = 3.6, $H1^{II}$), 4.756 (d, 1H, $J_{1I\text{-}2I}$ = 3.6, $H1^{I}$), 4.60 (overlappped with water, 1H, $H3^{I}$), 4.448 (dd, 1H, $J_{2I\text{-}3I}$ = 3.2, $H2^{I}$), 4.296 (dd, 1H, $J_{2II\text{-}3II}$ = 10.0, $H2^{II}$), 4.23-4.00 (m, 7H, $H6^{I}$, $H5^{I}$, $H6^{II}$, $H4^{I}$ and $H5^{II}$), 3.958 (dd, 1H, $J_{3II\text{-}4II}$ = 3.6, $J_{4II\text{-}5II}$ = 0.8, $H4^{II}$), 3.930 (dd, 1H, $H3^{II}$), 3.367 (s, 3H, CH_3O).

Step d: Methyl 2,6-di-O-benzyl-3,4-di-O-methyl-α-D-galactopyranosyl-(1→ 4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside

Following the standard deacetylation and methylation procedures, *methyl 3,4-di-O-acetyl-2,6-di-O-benzyl-α-D-galactopyranosyl-(1→ 4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside* (72 mg, 80.8 µmol) was converted into the title compound as colourless gum (62.7 mg, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): 7.35-7.08 (m, 25H, Ph), 5.717 (d, 1H, $J_{1II\text{-}2II}$ = 3.6, $H1^{II}$), 4.856 (d, 1H, J_{gem} = 11.2, a-$PhCH_2$), 4.843 (d, 1H, J_{gem} = 10.8, b-$PhCH_2$), 4.695 (d, 2H, J_{gem} = 12.0,

a-$PhCH_2$ and c-$PhCH_2$), 4.631 (d, 1H, J_{gem} = 12.4, d-$PhCH_2$), 4.571 (d, 1H, J_{gem} = 10.8, b-$PhCH_2$), 4.500 (d, 1H, J_{gem} = 12.4, d-$PhCH_2$), 4.450 (d, 1H, J_{gem} = 11.6, c-$PhCH_2$), 4.433 (d, 1H, J_{gem} = 11.2, e-$PhCH_2$), 4.359 (d, 1H, J_{gem} = 11.2, e-$PhCH_2$), 4.303 (d, 1H, J_{1I-2I} = 7.6, $H1^I$), 3.949 (t, 1H, J_{4I-3I} = 9.0, J_{4I-5I} = 9.0, $H4^I$), 3.871 (dd, 1H, $J_{5II-6axII}$ = 7.2, $J_{5II-6eqII}$ = 6.4, $H5^{II}$), 3.791 (dd, 1H, $J_{2II-3II}$ = 10.4, $J_{2II-1II}$ = 3.6, $H2^{II}$), 3.77-3.68 (m, 4H, $H4^{II}$, $H3^I$, H6ax^I and H6eq^I)), 3.59-3.53 (m, 2H, $H5^I$ and $H6^{II}$), 3.551 (s, 3H, OMe), 3.51-3.40 (m, 3H, $H3^{II}$, $H6^{II}$ and $H2^I$), 3.492 (s, 3H, OMe), 3.433 (s, 3H, OMe).

*Step e: Methyl 3,4-di-*O*-methyl-*α*-*D*-galactopyranosyl-(1→ 4)-*β*-*D*-glucopyranoside*

Following the standard debenzylation procedure, *methyl 2,6-di-*O*-benzyl-3,4-di-*O*-methyl-*α*-*D*-galactopyranosyl-(1→ 4)-2,3,6-tri-*O*-benzyl-*β*-*D*-glucopyranoside* (62.7 mg, 75.1 μmol) was deprotected to give the title compound as colourless gum (28 mg, 97%). ^{1}H NMR (D_2O, 400 MHz): 5.232 (d, 1H, $J_{1II-2II}$ = 4.4, $H1^{II}$), 4.217 (d, 1H, J_{1I-2I} = 8.0, $H1^I$), 3.83-3.75 (m, 3H, $H4^{II}$, $H5^{II}$ and $H6^I$), 3.682 (dd, 1H, $J_{2II-3II}$ = 10.4, $J_{2II-1II}$ = 4.4, $H2^{II}$), 3.64-3.52 (m, 4H, $H6^I$, $H3^{II}$ and $H6^{II}$), 3.47-3.38 (m, 3H, $H4^I$, $H5^I$ and $H3^{II}$), 3.400 (s, 3H, OMe), 3.340 (s, 6H, 2xOMe), 3.117 (dd, 1H, J_{2I-3I} = 9.6, J_{2I-1I} = 8.0, $H2^I$). ^{13}C NMR (D_2O, 100 MHz): 103.20, 99.64, 79.35, 76.92, 76.34, 75.35, 74.65, 73.06, 72.03, 68.00, 61.02, 60.89, 60.86, 57.30, 56.94.

*Step f: Methyl 3,4-di-*O*-methyl-2,6-di-*O*-sulfo-*α*-*D*-galactopyranosyl-(1→ 4)-2,3,6-tri-*O*-sulfo-*β*-*D*-glucopyranoside, pentasodium salt (PG2037)*

Following the standard sulfonation procedure, *methyl 3,4-di-*O*-methyl-*α*-*D*-galactopyranosyl-(1→ 4)-*β*-*D*-glucopyranoside* (28 mg, 72.8 μmol) gave the title compound (3.2 mg, 4.9%). ^{1}H NMR (400 MHz, D_2O): 5.357 (d, 1H, $J_{1II-2II}$ = 3.2, $H1^{II}$), 4.766 (d, 1H, J_{1I-2I} = 3.6, $H1^I$), 4.60 (overlappped with water, 1H, $H3^I$), 4.455 (dd, 1H, J_{2I-3I} = 2.8, $H2^I$), 4.304 (dd, 1H, $J_{2II-3II}$ = 10.0, $H2^{II}$), 4.22-3.99 (m, 5H, $H5^I$, $H6^I$, $H4^I$ and $H5^{II}$), 4.002 (d, 2H, $J_{5II-6II}$ = 6.8, $H6^{II}$), 3.886 (d, 1H, $J_{3II-4II}$ = 3.2, $H4^{II}$), 3.667 (dd, 1H, $H3^{II}$), 3.398 (s, 3H, CH_3O), 3.367 (s, 3H, CH_3O), 3.356 (s, 3H, CH_3O).

Example 4: PG2053 and PG2042

*Methyl 4-*O*-Allyl-2,3-di-*O*-sulfo-*α*-*L*-rhamnoside, disodium salt (PG2053).*

The title compound was obtained from *methyl 2,3-*O*-isopropylidene-*α*-*L*-rhamnopyranoside* [22] *via* the general alkylation (with allyl bromide) and deprotection procedure followed by the general sulfonation procedure, as a colourless powder. CE t_m = 10.48 min. ^{1}H NMR (400 MHz, D_2O) δ 1.19 (d, 3 H, $J_{5,6}$ 6.4 Hz; H-6), 3.26 (s, 3 H; OMe); 3.29-3.40 (m, 1 H; H-4), 3.59-3.67 (m, 1 H; H-5), 4.00-4.05, 4.18-4.22 (2 m, 2 H; OCH_2),

4.41-4.42 (m, 1 H; H-3), 4.63-4.64 (m, 2 H; H-2), 4.83 (s, 1 H; H-1), 5.07-5.21 (m, 2 H; $=CH_2$), 5.76-5.88 (m, 1 H; =CH).

When a reduced quantity (1 eq.) of SO_3•trimethylamine was employed, *methyl 4-O-allyl-2-O-sulfo-α-L-rhamnoside, sodium salt (PG2042)* was exclusively obtained. CE t_m > 25.00 min. ^{1}H NMR (400 MHz, D_2O) δ 1.19 (d, 3 H, $J_{5,6}$ 6.4 Hz; H-6), 3.16 (t, 1 H, $J_{3,4}$ 3.1, $J_{4,5}$ 9.7 Hz; H-4), 3.25 (s, 3 H; OMe), 3.54-3.58 (m, 1 H; H-5), 3.76 (dd, 1 H, $J_{2,3}$ 9.7 Hz; H-3), 4.03-4.18 (m, 2 H; OCH_2), 4.34-4.35 (m, 1 H; H-2), 4.80 (s, 1 H; H-1), 5.08-5.22 (m, 2 H; $=CH_2$), 5.78-5.88 (m, 1 H; =CH).

Example 5: PG2024

Methyl 4-O-Benzyl-2,3-di-O-sulfo-α-L-rhamnoside, disodium salt (PG2024)

The title compound was obtained from *methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside via* the general alkylation (with benzyl bromide) and deprotection procedure followed by the general sulfonation procedure, as a colourless powder. CE t_m = 10.82 min. ^{1}H NMR (400 MHz, D_2O) δ 1.00 (d, 3 H, $J_{5,6}$ 6.8 Hz; H-6), 3.23 (s, 3 H; OMe); 3.78-3.80 (m, 1 H; H-4), 3.88-3.94 (m, 1 H; H-5), 4.41-4.43 (m, 1 H; H-2), 4.52-4.56 (m, 2 H; H-3), 4.54, 4.78 (AB quartet, $J_{A,B}$ 12.0 Hz; CH_2Ph), 4.90 (dd, 1 H, $J_{1,2}$ 1.2 Hz; H-1), 7.20-7.36 (m, 5 H; ArH).

Example 6: PG2054

Step a: Methyl 4-O-benzoyl-α-L-rhamnoside

A solution of *methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside* (200 mg, 920 μmol), benzoyl chloride (193 mg, 1.38 mmol) and Et_3N (364 μL, 2.76 mmol) in DCM (10 mL) was stirred overnight. The resulting suspension (Et_3N•HCl precipitates) was diluted with DCM (50 mL) and washed with $NaHCO_3$ (sat. aqueous), water then brine, dried ($MgSO_4$) and evaporated. The residue was taken up in 50 mL of 1:1 MeCN:H_2O and p-TsOH (10 mg) was added. The resulting solution was stirred until the reaction was complete (TLC, ~4 h), evaporated and subjected to flash chromatography (1:1 EtOAc:hexanes) to give 165 mg (64 % over two steps) of the title compound as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03-8.00 (m, 2H, Hortho), 7.55 (tt, 1H, $J_{Hp\text{-}Hm}$ = 7.5, $J_{Hp\text{-}Ho}$ = 1.3, Hpara), 7.43-7.39 (m, 2H, Hmeta), 5.09 (dis t, 1H, $J_{4\text{-}3\text{-}4\text{-}5}$ = 9.3, H4), 4.73 (br s, 1H, H1), 4.01-3.97 (m, 2H, H2+H3), 3.91 (dq, 1H, $J_{4\text{-}5}$ = 9.7, $J_{5\text{-}6}$ = 6.4, H5), 3.53-3.46 (br s, 2H, OH), 3.38 (s, 3H, OMe), 1.25 (d, 3H, H6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.1, 133.3, 129.8, 129.5, 128.3, 100.6, 75.7, 70.8, 70.1, 65.7, 55.0, 17.4.

Step b: Methyl 4-O-Benzoyl-2,3-di-O-sulfo-α-L-rhamnoside, Disodium salt (PG2054)

The title compound was obtained from *methyl 4-O-benzoyl-α-L-rhamnoside via* the general sulfonation procedure as a colourless powder. CE t_m = 11.14 min. ^{1}H NMR (400 MHz, D_2O) δ 1.14 (d, 3 H, $J_{5,6}$ 6.3 Hz; H-6), 3.33 (s, 3 H; OMe), 3.99-4.07 (m, 1 H; H-5), 4.66-4.73 (m, 2 H; H-2, -3), 4.95 (d, 1 H, $J_{1,2}$ 1.4 Hz; H-1), 5.04 (t, 1 H, $J_{3,4=4,5}$ 9.6 Hz; H-4), 7.35-7.41, 7.53-7.55, 7.92-7.93 (3 m, 5 H; Ph).

Example 7: PG2041

Step a: 4,6-O-Benzylidene-1,2-dihydro-D-glucal.

A mixture of *tri-O-acetyl-D-glucal* (1.7 g, 6.25 mmol), AcOH (50 μL) and $Pd(OH)_2$/C (100 mg) in MeOH (15 mL) was vigorously stirred under H_2 (1 atm.) overnight. The mixture was filtered, the solvent evaporated and the residue subjected to flash chromatography (10-50% EtOAc/hexanes) to yield *tri-O-acetyl-1,2-dihydro-D-glucal* as a colourless oil. This residue was co-evaporated (2 × 10 mL MeCN) then subjected to the Zemplén deacetylation general procedure to yield *1,2-dihydro-D-glucal* as a colourless oil (825 mg, 89%). This residue was co-evaporated (2 × 10 mL MeCN).

p-TsOH.H_2O (50 mg) was added to a solution of the *1,2-dihydro-D-glucal* (495 mg, 3.34 mmol) and α,α-dimethoxytoluene (753 μL, 5.01 mmol) in DMF (5 mL) and the combined mixture stirred (60°, 1 h). Et_3N (100 μL) was introduced and the solvent was evaporated. The residue was subjected to flash chromatography (0-5% MeOH/$CHCl_3$) to yield the title compound as colourless needles (503 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72-2.01 (m, 2 H; H-2), 3.27-3.33 (m, 1 H; H-5), 3.41 (dd, 1 H, $J_{3,4}$ 8.8, $J_{5,6}$ 9.1 Hz; H-4), 3.49-3.56 (m, 1 H; H-3), 3.67 (t, 1 H, $J_{5,6=6,6}$ 10.3 Hz; H-6), 3.81-3.87, 3.93-3.98 (2 m, 2 H; H-1), 4.25 (dd, 1 H; $J_{5,6}$ 4.9 Hz; H-6), 5.53 (s, 1 H; C*H*Ph), 7.23-7.52 (m, 5 H, CHPh). ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.47 (C-2); 66.46, 69.07, 69.64, 71.32 (4 C; C-1,-4,-5,-6), 84.14, (C-3), 102.16 (*C*HPh), 126.43, 128.55, 129.34, 137.50 (4 C; Ph).

Step b: 3-O-Benzyl-4,6-di-O-sulfo-1,2-dihydro-D-glucal, Disodium salt (PG2041).

4,6-O-Benzylidene-1,2-dihydro-D-glucal was subjected to the alkylation (benzyl bromide), de-protection and sulfonation general procedures to yield the title compound as a colourless powder. CE t_m = 15.40 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48-1.53, 1.97-2.03 (2 m, 2 H; H-2), 3.30-3.71 (m, 1 H; H-1), 3.52-3.57 (m, 1 H; H-5), 3.60-3.66 (m, 1 H; H-3), 3.78-3.83 (m, 1 H; H-1), 3.97 (dd, 1 H, $J_{5,6}$ 8.0, $J_{6,6}$ 11.4 Hz; H-6), 3.98 (t, 1 H, $J_{3,4=4,5}$ 8.9 Hz; H-4), 4.34 (dd, 1 H, $J_{5,6}$ 2.3 Hz; H-6), 4.52-4.67 (m, 2 H; CH_2Ph), 7.21-7.36 (m, 5 H; Ph).

Example 8: PG2030

Step a: 1,6-Anhydro-3-O-methyl-β-D-glucopyranose.

p-Toluenesulfonyl chloride (790 mg, 4.14 mmol) was added to a cooled (0°) suspension of *3-O-methyl-D-glucopyranose* (804 mg, 4.14 mmol) in pyridine (10 mL) and the reaction mixture stirred (0°→ r.t, 1.5 h). Ac_2O (1.5 mL, 15 mmol) and *N,N*-dimethylaminopyrdine (50 mg) were then introduced and stirring continued (r.t., 4 h). The mixture was then cooled (0°) and MeOH (3 mL) was added and stirring maintained (10 min) prior to evaporation of the solvent. The residual oil was dissolved (EtOAc) and subjected to workup yielding the tosylate as a pale yellow coloured oil (1.93 g). A mixture of the crude tosylate (1.93 g) and NaOH (20 mL of 1.0 M, 20 mmol) in EtOH (20 mL) was heated (80°, 1 h). The mixture was neutralised with acetic acid and the solvent evaporated and co-evaporated (toluene). The crude residue was treated with pyridine (10 mL), Ac_2O (5 mL) and *N,N*-dimethylaminopyridine (50 mg) and the combined mixture stirred (r.t., o/n). The mixture was treated with ice-water (10 mL) and stirring continued (r.t., 3 h) before being subjected to workup (EtOAc). The residual oil was subjected to flash chromatography (20-50% EtOAc/hexanes) to yield an inseparable mixture of *2,4-di-O-acetyl-1,6-anhydro-3-O-methyl-β-D-glucopyranose* (**a**) and *1,2,4-tri-O-acetyl-3-O-methyl-6-O-tosyl-α-D-glucopyranose* (**b**) (in a ratio of 3:1) as a pale yellow oil (466 mg). The ratio was determined by integration of the H-1 and 3-OMe signals observed in the ^{1}H NMR spectrum. Partial ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 3 H; OMe **b**), 3.45 (s, 3 H; OMe **a**); 5.22 (br s, 1 H; H-1 **b**), 5.42 (br s, 1 H; H-1 **a**). The mixture of the two compounds (456 mg) was subjected to the Zemplén deacetylation general method and the residue subjected to flash chromatography (0-5% MeOH/EtOAc) to yield the title compound as a colourless oil (162 mg, 33%, 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.27-3.30 (m, 1 H; H-3), 3.38 (s, 3 H; OMe), 3.57-3.59 (m, 1 H; H-2), 3.63-3.65 (m, 1 H; H-4), 3.70 (dd, 1 H, $J_{5,6}$ = 5.6, $J_{6,6}$ = 7.2 Hz; H-6), 4.06 (d, 1 H, $J_{6,6}$ = 7.2 Hz; H-6), 4.48-4.51 (m, 1 H; H-5), 4.39 (br s, 1 H; H-1).

Step b: 1,6-Anhydro-4-O-benzyl-3-O-methyl-β-D-glucopyranose.

A mixture of *1,6-anhydro-3-O-methyl-β-D-glucopyranose* (155 mg, 0.88 mmol) and Bu_2SnO (241 mg, 0.97 mmol) in toluene (18 mL) was heated under reflux (with azeotropic removal of water) until the solution was one-half the original volume. The mixture was cooled (80°), BnBr (104 μL, 0.88 mmol) and Bu_4NBr (567 mg, 1.76 mmol) were introduced and stirring continued (o/n). The mixture was treated with MeOH (2 mL) and H_2O (1 mL) with continued stirring (10 min) prior to evaporation of the solvent. The residue was subjected to

workup (EtOAc) and flash chromatography (20-60% EtOAc/ hexanes) to yield two compounds.

Firstly, the title compound was produced as a colourless oil (94 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (d, 1 H, $J_{2,OH}$ 6.4 Hz; OH), 3.32-3.43 (m, 5 H; H-3, H-4, OMe), 3.52-3.57 (m, 1 H; H-2), 3.68-3.72, 4.01-4.04 (2 m, 2 H; H-6), 4.55-4.58 (m, 1 H; H-5), 4.64 (s, 2 H; CH_2Ph), 5.39-5.40 (m, 1 H; H-1), 7.28-7.36 (m, 5 H; ArH).

Secondly, *1,6-anhydro-2-*O*-benzyl-3-*O*-methyl-*β*-*D*-glucopyranose* was afforded as a colourless oil (91 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.90 (br s, 1 H; OH), 3.31-3.34 (m, 4 H; H-2, OMe), 3.36-3.38 (m, 1 H; H-3), 3.58 (br s, 1 H; H-4), 3.68 (dd, 1 H, $J_{5,6}$ 6.0 Hz, $J_{6,6}$ 7.2 Hz; H-6), 4.08 (dd, 1 H, $J_{5,6}$ 0.8 Hz, $J_{6,6}$ 7.2 Hz; H-6), 4.47-4.49 (m, 1 H; H-5), 4.56, 4.62 (AB quartet, $J_{A,B}$ 12.0 Hz; CH_2Ph), 5.40-5.41 (m, 1 H; H-1), 7.26-7.36 (m, 5 H; ArH).

*Step c: 1,6-Anhydro-4-*O*-benzyl-3-*O*-methyl-2-*O*-sulfo-*β*-*D*-glucopyranose, sodium salt (PG2030)*

*1,6-Anhydro-4-*O*-benzyl-3-*O*-methyl-*β*-*D*-glucopyranose* (84 mg, 0.32 mmol) was sulfonated according to the general procedure and subjected to flash chromatography (50/2/1→10/2/1 EtOAc/MeOH/H_2O) prior to SEC to yield the title compound as a pale yellow coloured powder (70 mg, 60%); CE t_m = 5.62 min; ^{1}H NMR (400 MHz, D_2O) δ 3.19 (s, 3 H; OCH_3); 3.43-3.45 (m, 1 H; H-4), 3.52-3.53 (m, 1 H; H-3), 3.57 (dd, 1 H, $J_{5,6}$ = 5.9 Hz, $J_{6,6}$ = 7.8 Hz; H-6), 3.82 (dd, 1 H, $J_{5,6}$ = 1.1 Hz, $J_{6,6}$ = 7.8 Hz; H-6), 3.97-3.99 (m, 1 H; H-5), 4.59-4.61 (m, 3 H; H-2, CH_2Ph), 5.41 (br s, 1 H; H-1), 7.22-7.34 (m, 5 H; ArH).

Example 9: PG2012 and PG2013

Step a: N*-benzyl-*N*-(cyclohexylacetamido)-1,2,3,4-tetra-O-acetyl-*D*-glucuronamide*

Following the general procedure for the Ugi reaction, D-glucuronic acid (0.950 g, 4.89 mmol), and solutions of each of the following three reagents: benzylamine (2 M in MeOH, 2.45 mL, 4.89 mmol), formaldehyde (2 M in MeOH, 2.45 mL, 4.89 mmol) and cyclohexylisocyanide (1 M in MeOH, 4.89 mL, 4.89 mmol) were loaded into a reaction vessel and the mixture stirred at r.t. for 19 h. The volatiles were removed under reduced pressure and dried under high vacuum to afford N*-benzyl-*N*-(cyclohexylacetamido)-*D*-glucuronamide* as a yellow foam.

Following the general procedure for acetylation, the above crude Ugi product was peracetylated to give the title compound as pale-yellow foam 1.929 g, 66% (two steps, Rf = 0.37, hexane-EtOAc 1:1) after flash chromatography (gradient elution with hexanes-EtOAc 2:1 to 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) was very complicated due to the presence of anomers and

rotamers. The spectrum was not simplified after the temperature was raised to 55 °C. However, in pyridine-d_6 at 100 °C, each set of rotamers was coalesced in some degree into much more simplified structure, thus two anomers were clearly observed (α:β ratio = 69:31). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): 7.41-7.14 (m, 5H, Ph), 6.337 (d, 0.39H, J= 3.6), 6.300 (d, 0.29H, J= 3.6), 5.969 (br d, 0.52H, J= 8), 5.823 (br d, 0.09H, J= 8.4), 5.66-5.41 (m, 2.25H), 5.28-5.09 (m, 1.3H), 4.92-4.58 (m, 2.25H), 4.411 (d, J = 10) and 4.395 (d, J = 14, 0.55H), 4.271 (d, 0.11H, J= 9.6), 4.219 (d, 0.09H, J= 17.2), 4.125 (d, 0.17H, J= 14), 4.098 (d, 0.17H, J = 14.4), 3.994 (d, J = 15.2) and 3.963 (d, J = 14.8, 0.89H), 3.82-3.59 (m, 2.04H), 2.190, 2.111, 2.038, 2.033, 2.025, 2.023, 2.016, 2.014, 2.008, 1.998, 1.983, 1.944 and 1.927 (all singlet, 12H, Ac), 1.89-1.55 (m, 5H, cyclohexyl-CH_2), 1.41-0.83 (m, 5H, cyclohexyl-CH_2). ^{1}H NMR ($CDCl_3$, 400 MHz, 55 °C): 7.38-7.16 (m, 5H, Ph), 6.336 (d, J= 3.2,) and 6.153 (d, J= 3.2, 0.7H), 5.939 (br d, 0.6H, J = 6.8), 5.721 (br d, 0.2H, J = 7.2), 5.65-5.55 (m, 1.3H), 5.52-5.41 (m, 1H,), 5.28-5.10 (m, 1.4H), 4.85-4.58 (m, 2.4H), 4.48-4.40 (m, 0.6H), 4.318 (d, 0.1H, J = 9.2), 4.205 (d, 0.1H, J = 17.6), 4.02-3.93 (m, 0.9H), 3.84-3.62 (m, 2.2H), 2.179, 2.090, 2.021, 2.012, 2.001, 1.989, 1.983, 1.975, 1.968, 1.959 and 1.935 (all singlet, 12H, Ac), 1.88-1.56 (m, 5H, cyclohexyl-CH_2), 1.42-0.88 (m, 5H, cyclohexyl-CH_2). ^{1}H NMR (pyridine-d_6, 400 MHz, δ7.22, 100 °C): only typical sugar protons are given; the remaining signals (except acetate singlets) were complicated and appeared as broad lumps. α-anomer, 6.672 (d, J = 3.6, glu-H1), 5.456 (dd, J = 9.6, 3.6, glu-H2); β-anomer, 6.206 (d, J = 8.0, glu-H1), 5.741 (t, J = 9.2, glu-H4 or H5), 5.515 (dd, J = 8.8, 8.0, glu-H2).

Step b: N-*benzyl*-N-*(cyclohexylacetamido)-1,2,3,4-tetra*-O-*sulfo*-α-D-*glucuronamide, tetrasodium salt (PG2012) and* N-*benzyl*-N-*(cyclohexylacetamido)-1,2,3-tri*-O-*sulfo*-α-D-*glucuronamide, trisodium salt (PG2013)*

Following the general procedure for deacetylation, the above tetraacete (0.441 g, 0.747 mmol) was deacetylated to give N-*benzyl*-N-*(cyclohexylacetamido)*-D-*glucuronamide* as pale-yellow glass (0.316 g, 100%).

Following the general procedure for sulfonation, the above tetrol (0.257 g, 0.608 mmol) was sulfonated (using sulfur trioxide pyridine complex, 60 °C, 19 h). The residue was co-evaporated with toluene and purified by flash chromatography [2.5 × 20cm, eluted with EtOAc, MeCN, MeCN-Et_3N (10:1), MeCN-Et_3N-H_2O (110:2:11)]. The fractions were divided into two parts according to TLC and CE. The less polar part was purified again by flash chromatography, LH20 (×2) and ion exchange chromatography to give trisulfate PG2013 as white fluffy powder after lyophilisation (19.3 mg, 4.4%). ^{1}H NMR (D_2O, 400 MHz): two

rotamers in a ratio of 56:44. major rotamer, δ 7.36-7.11 (m, 5H, Ph), 5.946 (d, 1H, J= 3.2, H1), 4.894 (d, 1H, J= 9.6, H5), 4.748 (d, 1H, J= 16, a-CH_2), 4.685 (d, 1H, J= 16, a-CH_2), 4.502 (t, 1H, J= 10.4, 9.6, H3), 4.306 (dd, 1H, J= 9.6, 3.6, H2), 4.005 (t, 1H, J= 9.6, 8.8, H4), 3.869 (s, 2H, b-CH_2), 3.42-3.32 (m, 1H, cyclohexyl-CHN), 1.64-1.36 (m, 5H, cyclohexyl-CH_2), 1.20-0.92 (m, 5H, cyclohexyl-CH_2); minor rotamer, 7.36-7.11 (m, 5H, Ph), 5.905 (d, 1H, J= 3.2, H1), 4.578 (d, 1H, J= 10, H5), 4.523 (s, 2H, c-CH_2), 4.478 (t, 1H, J= 10.4, 9.6, H3), 4.321 (d, 1H, J= 17.6, d-CH_2), 4.281 (dd, 1H, J= 9.6, 3.2, H2), 4.039 (t, 1H, J= 9.6, 9.2, H4), 3.900 (d, 1H, J = 17.6, d-CH_2), 3.42-3.32 (m, 1H, cyclohexyl-CHN), 1.64-1.36 (m, 5H, cyclohexyl-CH_2), 1.20-0.92 (m, 5H, cyclohexyl-CH_2). ^{13}C NMR (D_2O, 100 MHz, no reference): double-up of each signals due to two rotamers, 169.96 (amide-CON), 169.75 (amide-CON), 168.91 (amide-CON), 168.85 (amide-CON), 135.45 (*ipso*-Ph), 135.20 (*ipso*-Ph), 129.16, 129.07, 128.47, 128.32, 128.20 and 128.13 (*meta*-, *ortho*- and *para*-Ph), 95.67 and 95.65 (glu-C1), 77.84 and 77.75 (glu-C3), 73.76 and 73.71 (glu-C2), 70.66 and 70.18 (glu-C4), 69.23 and 68.70 (glu-C5), 52.87 (a-CH_2), 51.12 (c-CH_2), 50.32 (d-CH_2), 50.02 (b-CH_2), 49.25 and 49.00 (cyclohexyl-CHN), 31.89 and 31.86, 25.08 and 25.05, 24.47 and 24.38 (cyclohexyl-CH_2). ES-LRMS (+ve, *m/z*): $C_{21}H_{27}N_2Na_3O_{16}S_3$ required 728.02, found 751 ($M+Na^+$), 729 ($M+H^+$); ES-HRMS (+ve, *m/z*): $M+Na^+$, $C_{21}H_{27}N_2Na_4O_{16}S_3$ required 751.0113, found 750.1087; $M+H^+$, $C_{21}H_{28}N_2Na_3O_{16}S_3$ required 729.0294, found 729.0242.

The polar part was purified by LH20 column (×2) and ion exchange column to give tetrasulfate PG2012 as an off-white powder after lyophilisation (7.6 mg, 1.5%). ^{1}H NMR (D_2O, 400 MHz): two rotamers in a molar ratio of 70:30. Major rotamer, δ 7.34-7.16 (m, 5H, Ph), 5.954 (d, 1H, J= 3.6, H1), 5.235 (d, 1H, J= 9.6, H5), 4.904 (d, 1H, J= 15.6, a-CH_2), 4.67-4.57 (overlapped with water, 1H, H3), 4.536 (t, 1H, J= 9.6, 8.8, H4), 4.466 (d, 1H, J= 15.6, a-CH_2), 4.394 (dd, 1H, J= 9.8, 3.4, H2), 3.927 (d, 1H, J= 16.8, b-CH_2), 3.749 (d, 1H, J= 16.8, b-CH_2), 3.30-3.20 (m, 1H, cyclohexyl-CHN), 1.65-1.35 (m, 5H, cyclohexyl-CH_2), 1.18-0.92 (m, 5H, cyclohexyl-CH_2); minor rotamer, 7.34-7.16 (m, 5H, Ph), 5.912 (d, 1H, J= 3.4, H1), 4.77-4.72 (m, 2H, H5 and H3 or H4), 4.689 (d, 1H, J= 15.2, c-CH_2), 4.67-4.56 (overlapped with water, 1H, H4 or H3), 4.373 (dd, 1H, J= 9.8, 3.4, H2), 4.256 (d, 1H, J= 18.4, d-CH_2), 4.215 (d, 1H, J = 15.2, c-CH_2), 3.936 (d, 1H, J = 18.4, d-CH_2), 3.36-3.26 (m, 1H, cyclohexyl-CHN), 1.65-1.35 (m, 5H, cyclohexyl-CH_2), 1.18-0.92 (m, 5H, cyclohexyl-CH_2). ^{13}C NMR (D_2O, 100 MHz, no reference): major rotamer, 172.35 (amide-CON), 171.69 (amide-CON), 137.22 (*ipso*-Ph), 131.71 and 131.58 (*meta*- and *ortho*-Ph), 131.11 (*para*-Ph), 97.68 (glu-C1), 78.08 (glu-C4), 77.60 (glu-C3), 76.43 (glu-C2), 70.10 (glu-C5), 55.81 (a-CH_2), 53.17

(b-CH_2), 51.77 (cyclohexyl-CHN), 34.17 (cylcohexyl-CH_2), 27.56 (cylcohexyl-CH_2), 27.13 (cylcohexyl-CH_2); minor rotamer (only typical peaks shown), 97.65 (glu-C1), 78.22 (glu-C4), 77.77 (glu-C3), 76.33 (glu-C2), 71.01 (glu-C5), 53.26 (d-CH_2), 53.79 (c-CH_2), 52.10 (cyclohexyl-CHN), 34.28 (cylcohexyl-CH_2), 27.52 (cylcohexyl-CH_2), 27.08 (cylcohexyl-CH_2). ES-MS (+ve, *m/z*): $C_{21}H_{26}N_2Na_4O_{19}S_4$ required 829.96, found 853 ($M+Na^+$), 831 ($M+H^+$). ES-HRMS (+ve, *m/z*): $M+Na^+$, $C_{21}H_{26}N_2Na_5O_{19}S_4$ required 852.9501, found 852.9334; $M+H^+$, $C_{21}H_{27}N_2Na_4O_{19}S_4$ required 830.9682, found 830.9635.

Example 10: PG2064

Step a: 2-(N-acetyl-N-cyclohexyl)amino-N-(methyl 2,3,4-tri-O-benzyl-6-deoxy-α-D-mannopyranos-6-yl)acetamide

Following the general procedure for the Ugi reaction, a solution of each of the following four reagents: acetic acid (2 M in MeOH, 60 µL, 119 µmol), cyclohexylamine (2 M in MeOH, 60 µL, 119 µmol), formaldehyde (2 M in MeOH, 60 µL, 119 µmol) and *methyl 2,3,4-tri-O-benzyl-6-deoxy-6-isocyano-α-D-mannopyranoside* (0.721 M in $CHCl_3$, 150 µL, 108 µmol) was loaded into a 4 mL sample vial and the mixture stirred at 60 °C for 19 h. The volatiles were removed under reduced pressure and purified by flash chromatography (gradient elution with hexane-EtOAc 4:1 to 1:4) to afford the title compound as a colourless gum, 42 mg, 60% (Rf = 0.49, EtOAc). ^1H NMR ($CDCl_3$, 400 MHz): two rotamers in a ratio of 72:28. δ 7.38-7.26 (m, 15H, 3 × C_6H_5), 6.933 (t, 72% × 1H, J = 4.4, NH in major rotamer), 6.357 (t, 28% × 1H, J = 5.8, NH in minor rotamer), 4.91-4.41 (m, 7H, sugar-H1 and 3 × $PhCH_2$), 4.04-3.42 (m, 9H, sugar-H2-6, NCH_2CO and cyclohexyl-CH), 3.305 (s, 72% × 3H, CH_3O in major rotamer), 3.266 (s, 28% × 3H, CH_3O in minor rotamer), 2.067 (s, 72% × 3H, CH_3CO in major rotamer), 2.012 (s, 28% × 3H, CH_3CO in major rotamer), 1.85-1.00 (m, 10H, cyclohexyl-CH_2).

Step b. 2-(N-acetyl-N-cyclohexyl)amino-N-(methyl 6-deoxy -2,3,4-tri-O-sulfo-α-D-mannopyranos-6-yl)acetamide, trisodium salt (PG2064)

Following the general procedure for deprotection of benzyl ethers, a mixture of the above tribenzyl ether (42 mg, 0.065 mmol), 20% palladium on activated charcoal (22 mg) in MeOH (2 mL) was stirred under hydrogen atmosphere at 50 psi for 10 h. General work-up gave the triol intermediate as a colourless gum. Following the general procedure for sulfonation, the triol was sulfonated (sulfur trioxide trimethylamine complex, 60 °C, 19 h) and the crude was evaporated. The residue was purified via sequential SEC (Bio Gel P-2 followed by LH20). The pure product was converted to the sodium salt by passing through an ion

exchange column to give the title compound as a white fluffy powder after lyophilisation (3.1 mg, 7.0%, two steps). ^{1}H NMR (D_2O, int. ref. acetone at 2.05, 400 MHz): two rotamers in a ratio of 63:37. δ 4.844 (s, 1H, sugar-H1), 4.678 (s, 1H, sugar-H2), 4.51-4.45 (m, 1H, sugar-H3), 4.240 (t, 37% × 1H, J = 9.6, sugar-H4 in minor rotamer), 4.214 (t, 63% × 1H, J = 9.6, sugar-H4 in major rotamer), 3.980 (s, 37% × 2H, $COCH_2N$ in minor rotamer), 3.825 (s, 63% × 2H, $COCH_2N$ in major rotamer), 3.78-3.59 (m, 3H, sugar-H5, one sugar-H6 and cyclohexyl-CH), 3.31-3.17 (m, 4H, one sugar-H6 and CH_3O [3.253, s, 3H]), 2.060 (s, 67% × 3H, CH_3CO in major rotamer), 1.900 (s, 33% × 3H, CH_3CO in minor rotamer), 1.70-0.88 (m, 10H, cyclohexyl-CH_2).

Example 11: PG2068

Step a.

Following the general procedure for the Ugi reaction, monomethyl succinate (15.7 mg, 0.119 mmol) and a solution of each of the following three reagents: ethylamine (2 M in MeOH, 60 μL, 119 μmol), formaldehyde (2 M in MeOH, 60 μL, 119 μmol) and *methyl 2,3,4-tri-O-benzyl-6-deoxy-6-isocyano-α-D-mannopyranoside* (0.721 M in $CHCl_3$, 150 μL, 108 μmol) was loaded into a 2 mL sample vial and the mixture stirred at r.t. for 19 h. The volatiles were removed under reduced pressure and purified by flash chromatography (gradient elution with hexane-EtOAc 1:1 to 1:4 then EtOAc) to afford pure product as a colourless gum (46.8 mg, 65%). ^{1}H NMR ($CDCl_3$, 400 MHz): two rotamers in a ratio of 73:27. δ 7.38-7.25 (m, 15H, Ph), 6.598 (t, 73% × 1H, J = 6, NH), 6.529 (t, 27% × 1H, J = 6, NH), 4.93-4.61 (m, 7H, sugar-H1 and 3 × $PhCH_2$), 4.14-3.24 (m, 16H, sugar 6 × H, NCH_2CO, 2 × CH_3O [singlets at 3.660 and 3.301, 73%; 3.648 and 3.276, 27%] and ethyl-CH_2), 2.70-2.42 (m, 4H, $COCH_2CH_2CO$), 1.138 (t, 73% × 3H, J = 7, ethyl-CH_3), 1.014 (t, 27% × 3H, J = 7, ethyl-CH_3). ^{13}C (100 MHz, $CDCl_3$, δ 77.0): major rotamer, 173.32, 171.73, 168.94, 138.20, 138.17, 138.09, 128.22, 128.18, 128.10, 127.76, 127.63, 127.49, 127.46, 98.94, 79.97, 75.38, 75.01, 74.84, 73.01, 72.01, 70.10, 54.63, 51.63, 49.84, 43.59, 39.63, 28.99, 27.24, 13.45. minor rotamer (only non-overlapped peaks), 173.26, 171.54, 168.01, 128.27, 127.69, 127.55, 98.98, 79.85, 75.14, 74.40, 72.86, 71.92, 69.97, 54.74, 50.91, 49.72, 42.10, 28.90, 27.83, 12.29.

Step b. (PG2068)

Following the general procedure for deprotection of benzyl ethers, a mixture of the above tribenzyl ether (46.8 mg, 0.0706 mmol), 20% palladium on activated charcoal (30 mg) in MeOH (3 mL) was stirred under hydrogen atmosphere at 50 psi for 2 h. General work-up gave

the triol intermediate as a colourless gum. Following the general procedure for sulfonation, the triol was sulfonated (sulfur trioxide trimethylamine complex, 60 °C, 19 h). The residue was dissolved in 1M NaOH (3 mL, 0.16 M). The mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was purified via sequential SEC (Bio-Gel P-2 followed by LH20). The pure product was converted into the sodium salt by passing through an ion exchange column to give the PG2068 as a white powder (4.9 mg, 9.8%, two steps). ^{1}H NMR (D_2O, int. ref. acetone at 2.05, 400 MHz): two rotamers in a ratio of 70:30. δ 4.86-4.84 (m, 1H, sugar-H1), 4.69-4.67 (m, 1H, sugar-H2), 4.50-4.46 (m, 1H, sugar-H3), 4.28-4.19 (m, 1H, sugar-H4), 4.072 (s, 30% × 2H, 2H of $COCH_2N$ in minor rotamer), 3.987 (d, 35% × 2H, J = 16.8, 1H of $COCH_2N$ in major rotamer), 3.815 (d, 35% × 2H, J = 16.8, 1H of $COCH_2N$ in major rotamer), 3.79-3.69 (m, 2H, sugar-H5 and one sugar-H6), 3.44-3.18 (m, 6H, one sugar-H6, ethyl-CH_2 and CH_3O [3.245, s, 3H]), 2.633 (t, J = 6.8) and 2.45-2.37 (m, total 4H, $COCH_2CH_2CO_2$), 1.054 (t, 70% × 3H, J = 7.2, CH_3O), 0.906 (t, 30% × 3H, J = 7.2, CH_3O).

Example 12: PG2075

Step a

3-Chlorophenylacetic acid (223 mg, 1.307 mmol) was dissolved in MeCN (3 mL). Ammonia solution (28%, 0.26 mL, 3.8 mmol) was added. The mixture was swirled for a while and evaporated *in vacuo*. The residue was suspended in MeCN (3 mL), filtered and the white solid was washed with MeCN and freeze-dried to afford ammonium 3-chlorophenylacetate (0.195 g, 80%).

Following the general procedure for the Ugi reaction, the above ammonium salt (22.5 mg, 0.120 mmol) and a solution of each following two reagents: formaldehyde (2 M in MeOH, 60 µL, 119 µmol) and *2-isocyanoethyl 2,3,4,6-tetra*-O-*benzyl*-α-D-*mannopyranoside* (0.762 M in $CHCl_3$, 157 µL, 120 µmol) was loaded into a 2 mL sample vial and the mixture stirred at r.t. for 19 h. The volatiles were removed under reduced pressure and the residue purified by flash chromatography to give the product as a colourless gum (34.8 mg, 37%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.06 (m, 24H, 4 × C_6H_5 and 1 × C_6H_4), 6.731 (t, 1H, J = 6.0, NH), 4.878 (d, 1H, J = 10.8, a-CH_2), 4.844 (d, 1H, J = 2.0, sugar-H1), 4.770 (d, 1H, J = 12.4, b-CH_2), 4.723 (d, 1H, J = 12.4, b-CH_2), 4.640 (s, 2H, c-CH_2), 4.589 (d, 1H, J = 11.6, d-CH_2), 4.535 (d, 1H, J = 11.6, d-CH_2), 4.505 (d, 1H, J = 10.8, a-CH_2), 4.446 (d, 1H, J = 14.8, e-CH_2), 4.362 (d, 1H, J = 14.8, e-CH_2), 3.90-3.51 (m, 12H), 3.38-3.29 (m, 1H). ^{13}C (100 MHz, $CDCl_3$, δ 77.0): 169.67, 166.81, 138.27, 138.11, 137.70, 135.16, 134.31, 129.82, 129.40, 128.34, 128.31, 128.01,

127.85, 127.78, 127.70, 127.68, 127.60, 127.53, 127.46, 98.90, 79.96, 75.08, 75.04, 74.71, 73.58, 72.73, 72.19, 72.13, 69.78, 68.49, 63.17, 40.25, 39.27.

Step b (PG2075)

Following the general procedure for deprotection of benzyl ethers, a mixture of the above tetrabenzyl ether (34.8 mg, 0.0439 mmol), 20% palladium on activated charcoal (26 mg) in MeOH (2 mL) was stirred under hydrogen atmosphere at 50 psi for 2 h. General work-up gave the tetrol intermediate as a colourless gum. Following the general procedure for sulfonation, the above tetrol was sulfonated . The residue was purified via SEC (Bio-Gel P-2). The pure product was converted into the sodium salt by passing through an ion exchange column to give PG2075 as a white fluffy powder after lyophilisation (10.6 mg, 28%, two steps). ^{1}H NMR (D_2O, int. ref. acetone at 2.05, 400 MHz): δ 7.30-7.11 (m, 4H, Ar), 5.00-4.97 (m, 1H, sugar-H1), 4.72-4.28 (m, 3H, sugar-H2, H3 and H4), 4.21-3.30 (m, 11H, sugar-H5, H6 and 4 × CH_2).

Example 13: PG2014

Step a:

Following the general procedure for the Ugi reaction, *2-(benzyl3,4,6-tri*-O-*benzyl*-α-D-*mannopyranoside-2-yl)acetic acid* (50 mg, 0.0835 mmol) and a solution of each following three reagents: benzylamine (2 M in MeOH, 41.8 μL, 0.0835 mmol), formaldehyde (2 M in MeOH, 41.8 μL, 0.0835 mmol) and *2-isocyanoethyl 2,3,4,6-tetra*-O-*benzyl*-α-D-*mannopyranoside* (0.415 M in MeOH, 201.4 μL, 0.0835 mmol) was loaded into a 2 mL sample vial and the mixture stirred at r.t. for 19 h. General work-up gave the product as a colourless gum (38.9 mg, 36%). ^{1}H NMR (400 MHz): two rotamers around amide CO-NH single bond in a ratio of 66:34. δ 7.40-7.05 (m, 45H, 9 × C_6H_5), 6.66 (t, 0.66H, J = 5.6, CONH-major rotamer) and 6.40 (t, 0.34H, J = 5.4, CONH-minor rotamer), 5.104 (d, 0.66H, J = 1.2, H1^1-major rotamer) and 5.046 (s, 0.34H, H1^1-minor rotamer), 4.86-4.20 (m, 21H), 3.97-3.48 (m, 16H), 3.36 (q, 0.66H, J = 5.6, major rotamer) and 3.26 (q, 0.34H, J = 5.6, minor rotamer).

Step b (PG2014).

Following the general procedure for the deprotection of benzyl ethers, a mixture of the above octabenzyl ether (35 mg, 0.0267 mmol) and 20% palladium on activated charcoal (10 mg) in EtOH (4 mL) was stirred under hydrogen atmosphere at 50 psi for 2 h. General work-up gave the octol intermediate as a colourless gum. Following the general procedure for sulfonation, the above octol was sulfonated (sulfur trioxide trimethylamine complex, 60 °C, 19 h). The residue was purified via SEC (Bio-Gel P-2). The pure product was converted into the

sodium salt by passing through an ion exchange column to give PG2014 as a white powder (16.6 mg, 44%, two steps). ^{1}H NMR (D_2O, 400 MHz, complicated due to two rotamers): δ 7.32-7.14 (m, 5H, Ph), 5.80-5.66 (m, 0.5H), 5.44-5.39 (m, 0.5H), 5.04-4.96 (m, 1.5H), 4.80-4.20 (m, 9H, overlapped with water), 4.18-3.78 (m, 7.5H), 3.76-3.46 (m, 1.5H), 3.42-2.98 (m, 3.5H).

Example 14: PG2016

Step a.

Following the general procedure for the Ugi reaction, *trans*-1,4-diaminocyclohexane (6.3 mg, 0.055 mmol) and a solution of each following three reagents: *2-(methyl 2,3,4-tri-O-benzyl*α*-D-mannopyranoside-6-yl)acetic acid* (0.91 M in MeOH, 121 μL, 0.11 mmol), formaldehyde (2 M in MeOH, 55 μL, 0.11 mmol) and cyclohexylisocyanide (1 M in MeOH, 110 μL, 0.11 mmol) was loaded into a 2 mL sample vial and the mixture stirred at r.t. for 5 days. The volatiles were removed under reduced pressure and purified by flash chromatography (gradient elution with hexanes-EtOAc 2:1 to 1:4) to give the product as a colourless gum, 33.0 mg, 43% (Rf = 0.24, DCM-MeOH 95:5 or Rf = 0.48, MeCN-EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz, very complicated due to rotamers): δ 7.50-7.20 (m, 30H, Ph), 6.62 (br s, 1.1H), 6.48 (br s, 0.38H), 5.96 (br d, 0.26H, J = 8), 5.79 (br d, 0.26H, J = 10), 4.92-4.85 (m, 2H), 4.78-4.56 (m, 12H), 4.28-4.22 (m, 2.8H), 4.35-4.06 (m, 1.6H), 3.94-3.56 (m, 19.6H), 3.28 (s, 6H, OMe), 1.88-1.42 (m, 16H), 1.36-1.00 (m, 12H).

Step b. (PG2016).

Following the general procedure for the deprotection of benzyl ethers, a mixture of the above hexabenzyl ether (33 mg, 0.0235 mmol) and 20% palladium on activated charcoal (65 mg) in MeOH (2.8 mL) was stirred under hydrogen atmosphere at 1 atm for 5 days. General work-up gave the hexol intermediate as a colourless gum. Following the general procedure for sulfonation, the above hexol was sulfonated. The residue was purified via sequential column chromatography (SEC on Bio-Gel P-2 followed by ion exchange column) to give PG2016 as a white powder (12.2 mg, 35%). ^{1}H NMR (D_2O, 400 MHz): δ 4.97-4.92 (m, 2H, man-H1), 4.77-4.75 (m, 2H, man-H2), 4.58-4.52 (m, 2H, man-H3), 4.46-4.08 (m, 6H, containing man-H4 at 4.46-4.36, and OCH_2CO), 3.98-3.80 (m, 8H, man-H5, man-H6 and NCH_2CO), 3.80-3.32 (m, 6H, containing man-H6 at 3.80-3.64, and cyclohexyl-CH), 3.318 (s, 6H, OMe), 1.82-1.34 (m, 18H, cyclohexyl-CH_2), 1.26-1.00 (m, 10H, cyclohexyl-CH_2). ES-MS (+ve, *m/z*): $C_{40}H_{62}N_4Na_6O_{34}S_6$ required 1472.10, found 1495 ($M+Na^+$), 1473 ($M+H^+$). ES-HRMS (+ve,

m/z): M+Na^+, $C_{40}H_{62}N_4Na_7O_{34}S_6$ required 1495.0853, found 1495.0957; M+H^+, $C_{40}H_{63}N_4Na_6O_{34}S_6$ required 1473.1034, found 1473.1082.

Example 15: PG2015

Step a.

Following the general procedure for the Ugi reaction, 3,3-dimethylglutaric acid (7.1 mg, 0.0443 mmol) and a solution of each following three reagents: *3-aminopropyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside* (0.642 M in MeOH, 138 μL, 0.0886 mmol), formaldehyde (2 M in MeOH, 44.3 μL, 0.0886 mmol) and cyclohexylisocyanide (1 M in MeOH, 88.6 μL, 0..0886 mmol) were loaded into a 2 mL sample vial and the mixture stirred at r.t. for 5 days. The volatiles were removed under reduced pressure and purified by flash chromatography (gradient elution with hexanes-EtOAc 2:1 to 1:4) to give the product as a colourless gum, 32.3 mg, 46% (Rf = 0.45, hexane-EtOAc 1:3). ^{1}H NMR ($CDCl_3$, 400 MHz, very complicated due to rotamers): δ 7.38-7.21 (m, 40H, Ph), 7.003 (d, 0.41H, *J* = 7.7), 6.930 (br s, 0.21H), 6.726 (d, 0.4H, *J* = 8.4), 6.597 (d, 0.73H, *J* = 8.8), 6.487 (br s, 0.25H), 4.85-4.78 (m, 4H), 4.76-4.59 (m, 10H), 4.54-4.45 (m, 4H), 4.00-3.62 (m, 20H), 3.46-3.14 (m, 6H), 2.52-2.22 (m, 4H), 1.90-1.52 (m, 15H), 1.34-1.00 (m, 15H).

Step b. (PG2015).

Following the general procedure for the deprotection of benzyl ethers, a mixture of the above hexabenzyl ether (32.3 mg, 0.0202 mmol), 20% palladium on activated charcoal (41 mg) in MeOH (2.8 mL) was stirred under hydrogen atmosphere at 1 atm for 5 days. General work-up gave the octol intermediate as a colourless gum. Following the general procedure for sulfonation, the above octol was sulfonated. The residue was purified via SEC (Bio-Gel P-2) to give PG2015 as a white powder (12.6 mg, 37%). ^{1}H NMR (D_2O, 400 MHz): δ 5.020 (d, 2H, *J* = 1.6, man-H1), 4.759 (br s, 2H, man-H2), 4.66-4.56 (m, 2H, man-H3, overlapped with water), 4.46-4.41 (m, 2H, man-H6), 4.265 (t, 2H, *J* = 9.6, 9.2, man-H4), 4.10-3.96 (m, 4H, man-H5 and man-H6), 4.05-3.14 (m, 14H, NCH_2CO, cyclohexyl-CH and $NCH_2CH_2CH_2O$), 2.50-2.11 (m, 4H, CCH_2CO), 1.84-1.42 (m, 14H, cyclohexyl-CH_2 and $NCH_2CH_2CH_2O$), 1.24-0.93 (m, 16H, cyclohexyl-CH_2 and Me). ES-MS (+ve, *m/z*): $C_{41}H_{93}N_{11}O_{37}S_7$ (7 × SO_3NH_4) required 1556, found 1578 (M+Na^+), 1556 (M+H^+). ES-HRMS (+ve, *m/z*): M+H^+ $C_{41}H_{93}N_{11}O_{37}S_7$ required 1556.3857, found 1556.3783.

Additional compounds were synthesized using appropriate modifications of the syntheses detailed above in Examples 1 to 15. These additional compounds are included in the tables giving the results of biological testing of compounds according to the invention.

Example 16

Biological Testing of Compounds

Methods

Binding affinities of ligands for the growth factors were measured using a surface plasmon resonance (SPR) based solution affinity assay. The principle of the assay is that heparin immobilised on a sensorchip surface distinguishes between free and bound growth factor in an equilibrated solution of the growth factor and a ligand. Upon injection of the solution, the free growth factor binds to the immobilised heparin, is detected as an increase in the SPR response and its concentration thus determined. A decrease in the free growth factor concentration as a function of the ligand concentration allows for the calculation of the dissociation constant, K_d. It is important to note that ligand binding to the growth factors can only be detected when the interaction involves the heparin binding site, thus eliminating the chance of evaluating non-specific binding to other sites on the protein. A 1:1 stoichiometry has been assumed for all protein:ligand interactions.

The preparation of heparin-coated sensorchips, via immobilisation of biotinylated BSA-heparin on a streptavidin-coated sensorchip, has been described [23]. Heparin has also been immobilised via aldehyde coupling using either adipic acid dihydrazide or 1,4-diaminobutane. For each K_d measurement, solutions were prepared containing a fixed concentration of protein and varying concentrations of the ligand in buffer. Ligands binding to FGF-1 and VEGF were measured in HBS-EP buffer (10 mM HEPES, pH 7.4, 150 mM NaCl, 3.0 mM EDTA and 0.005% (v/v) polysorbate 20), while binding to FGF-2 was measured in HBS-EP buffer containing 0.3 M NaCl [23]. Prior to injection, samples were maintained at 4 °C to maximise protein stability. For each assay mixture, 50-200 µL of solution was injected at 5-40 µL/min and the relative binding response measured. All surface binding experiments were performed at 25 °C. The surface was regenerated by injection of 40 µL of 4M NaCl at 40 µL/min, followed by injection of 40 µL of buffer at 40 µL/min.

Sensorgram data were analysed using the BIAevaluation software (BIAcore). Background sensorgrams were subtracted from experimental sensorgrams to produce curves of specific binding, and baselines were subsequently adjusted to zero for all curves. The relative binding response for each injection was converted to free protein concentration using the equation

$$[P]=\frac{r}{r_m}[P]_{total}$$

where r is the relative binding response and r_m is the maximal binding response.

Binding equilibria established in solution prior to injection were assumed to be of 1:1 stoichiometry. Therefore, for the equilibrium,

$$P + L \rightleftharpoons P{\cdot}L$$

where P corresponds to the growth factor protein, L is the ligand, and $P{\cdot}L$ is the protein:ligand complex, the equilibrium equation is

$$K_d = \frac{[P][L]}{[P \cdot L]}$$

and the binding equation [23] can be expressed as

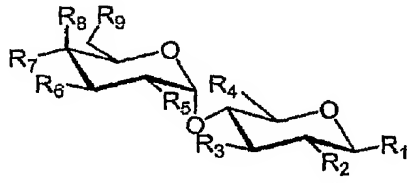
$$[P] = [P]_{total} - \frac{(K_d + [L]_{total} + [P]_{total})}{2} + \sqrt{\frac{(K_d + [L]_{total} + [P]_{total})^2}{4} - [L]_{total}[P]_{total}}$$

The K_d values given are the values fit, using the binding equation, to a plot of $[P]$ versus $[L]_{total}$. Where K_d values were measured in duplicate, the values represent the average of the duplicate measurements. It has been shown that GAG mimetics that bind tightly to these growth factors elicit a biological response *in vivo* [23].

Results

The results of the tests as described in the preceding section are presented in Tables 1 to 4.

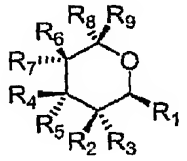
Table 1



	PG #	Kd aFGF	Kd bFGF	Kd VEGF	Kd FGF-4
R_1,R_6,R_8,R_9=OMe; R_2,R_3,R_5=OSO_3Na; R_4=CH_2OSO_3Na; R_7=H	2019	218 µM	657 µM		912 µM
R_1,R_6,R_8=OMe; R_2,R_3,R_5,R_9=OSO_3Na; R_4=CH_2OSO_3Na; R_7=H	2037	47.7 µM	507 µM	645 µM	

R_6,R_8,R_9=OH; R_1=OMe; R_2,R_3,R_5=OSO_3Na; R_4=CH_2OSO_3Na; R_7=H	2038	77.9 µM	2.10 mM	368 µM
R_1=OMe; R_6,R_8=OH; R_2,R_3,R_5,R_9=OSO_3Na; R_4=CH_2OSO_3Na; R_7=H	2039	21.8 µM	3.50 mM	1.27 mM
R_6,R_7,R_9=OH; R_4-R_1=-CH_2O-; R_2,R_5=$NHSO_3Na$; R_3=OBn; R_8=H	2046	6.35 mM	3.70 mM	1.50 mM
R_6,R_7,R_9,R_3=OH; R_4-R_1=-CH_2O-; R_2,R_5=$NHSO_3Na$; R_8=H	2047	388 µM	1.95 mM	2.55 mM
R_6,R_8,R_9=OH; R_1=OMe; R_2,R_3,R_5=OSO_3Na; R_4,R_7=H	2063	1.39 mM	2.35 mM	2.59 mM

Table 2

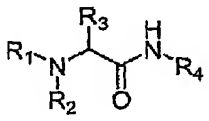


5

	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_1=OMe; R_3,R_5=OSO_3Na; R_7=OBn; R_8=CH_3; R_2,R_4,R_6,R_9=H	2023	1.76 mM	4.90 mM	2.27 mM
R_1=OMe; R_3,R_5=OSO_3Na; R_6=OBn; R_8=CH_3; R_2,R_4,R_7,R_9=H	2024	293 µM	250 µM	57.7 µM
R_1=OMe; R_3,R_4=OBz; R_7=OSO_3Na; R_9=CH_2OSO_3Na; R_2,R_5,R_6,R_8=H	2028	558 µM	12.0 mM	>> 1.65 mM
R_1=OMe; R_3,R_5=OSO_3Na; R_7=Oallyl; R_8=CH_3; R_2,R_4,R_6,R_9=H	2029	1.34 mM	> 10.00 mM	236 µM
R_9-R_1= -CH_2O-; R_3=OSO_3Na; R_4=OMe; R_7=OBn; R_2,R_5,R_6,R_8=H	2030	317 µM	4.61 mM	
R_4=$OCH_2CH_2CH_2OPh$;R_7=OSO_3Na; R_9=CH_2OSO_3Na; R_1,R_2,R_3,R_5,R_6,R_8=H	2040	12.9 mM	7.50 mM	2.44 mM
R_4=OBn;R_7=OSO_3Na; R_9=CH_2OSO_3Na; R_1,R_2,R_3,R_5,R_6,R_8=H	2041	9.38 mM	5.10 mM	1.04 mM
R_1=OMe; R_3=OSO_3Na; R_5=OH; R_6=Oallyl; R_8=CH_3; R_2,R_4,R_7,R_9=H	2042	3.05 mM	10.7 mM	2.59 mM
R_4=OMe;R_7=OSO_3Na; R_9=CH_2OSO_3Na; R_1,R_2,R_3,R_5,R_6,R_8=H	2043	6.43 mM	17.4 mM	1.73 mM
R_1=OMe; R_3,R_5=OSO_3Na; R_6=$OCOCH_2CH_2Ph$; R_8=CH_3; R_2,R_4,R_7,R_9=H	2044	366 µM	1.55 mM	1.65 mM
R_1=OMe as 1:1 anomeric mixture; R_9-R_4= -CH_2O-; R_3=OSO_3Na; R_7=OBn; R_2,R_5,R_6,R_8=H	2045	392 µM	3.40 mM	1.07 mM

	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_1=OMe R_4,R_3=OH; R_7=OSO_3Na; R_9=CH_2OSO_3Na; R_2,R_5,R_6,R_8=H	2048	233 μM	5.30 mM	796 μM
R_1=OMe R_4,R_3=OBn; R_7=OSO_3Na; R_9=CH_2OSO_3Na; R_2,R_5,R_6,R_8=H	2049	1.51 mM	>> 60.0 μM	2.72 mM
R_1=OMe; R_3 =OSO_3Na; R_4,R_7=OBn; R_2,R_5,R_6,R_8,R_9=H	2050	3.31 mM	8.25 mM	~ 10.00 mM
R_1=OMe; R_3,R_4=OBn; R_7=OSO_3Na; R_2,R_5,R_6,R_8,R_9=H	2051	2.46 mM	> 20.4 mM	4.63 mM
R_1=OMe; R_3,R_5=OSO_3Na; R_6=$OCOCH_2OPh$; R_8=CH_3; R_2,R_4,R_7,R_9=H	2052	5.92 mM	4.50 mM	686 μM
R_1=OMe; R_3,R_5=OSO_3Na; R_6=Oallyl; R_8=CH_3; R_2,R_4,R_7,R_9=H	2053	1.84 mM	5.10 mM	423 μM
R_1=OMe; R_3,R_5=OSO_3Na; R_6=OBz; R_8=CH_3; R_2,R_4,R_7,R_9=H	2054	454 μM	2.73 mM	403 μM
R_1=OMe; R_3,R_5=OSO_3Na; R_6=OCOPh(*p*-OMe); R_8=CH_3; R_2,R_4,R_7,R_9=H	2056	797 μM	2.45 mM	485 μM
R_9-R_4= -CH_2O-; R_2=OSO_3Na; R_7=OBn; R_1,R_3,R_5,R_6,R_8=H	2079		3.45 mM	
R_9-R_4= -CH_2O-; R_3=OSO_3Na; R_7=OBn; R_1,R_2,R_5,R_6,R_8=H	2080		11.6 mM	

Table 3

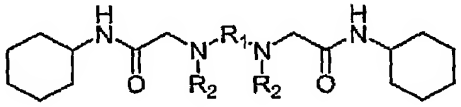


	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_1=1,2,3,4-tetra-*O*-sodium sulfo-D-glucuronoyl; R_2=$CH_2CH_2OSO_3Na$; R_4=cyclohexyl; R_3=H	2007	2.34 mM		
R_1=1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl-acetyl; R_2=$CH_2CH_2OSO_3Na$; R_3=H ; R_4=cyclohexyl	2008	296 μM	551 μM	335 μM
R_1=3-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-propyl; R_2=$COCH_2CH_2Ph$; R_4=cyclohexyl; R_3=H	2010	556 μM		
R_1=1,2,3,4-tetra-*O*-sodium sulfo-D-glucuronoyl; R_2=Bn; R_4=cyclohexyl; R_3=Ph	2011	62.4 μM		
R_1=1,2,3,4-tetra-*O*-sodium sulfo-α-D-glucuronoyl; R_2=Bn; R_4=cyclohexyl; R_3=H	2012	122 μM	505 μM	
R_1=1,2,3-tri-*O*-sodium sulfo-α-D-glucuronoyl; R_2=Bn; R_4=cyclohexyl; R_3=H	2013	587 μM	1.16 mM	
R_1=3-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-propyl; R_2= $CO(CH_2)_3Ph$; R_3=H; R_4=cyclohexyl	2018			

	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_1=1,2,3,4-tetra-*O*-sodium sulfonato-α-D-glucuronoyl; R_2,R_4=Bn; R_3=H	2020	104 μM	206 μM	437 μM
R_1=1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl-acetyl; R_2=Bn; R_4=cyclohexyl; R_3=H	2032	260 μM	201 μM	705 μM
R_1=Ac; R_2=Bn; R_3=H; R_4=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-ethyl	2035	24.8 μM	287 μM	76.6 μM
R_1=Ac; R_2=Bn; R_3=H; R_4=2-(2,3,4,6-tetra-*O*-sodium sulfo-β-D-mannopyranos-1-O-yl)-ethyl	2036	118 μM	2.50 mM	1.10 mM
R_1=Ac; R_2=CH_2CH_2Ph; R_3=H; R_4=6-deoxy-1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl	2058	224 μM	682 μM	109 μM
R_1=Ac; R_2=Bn; R_3=H; R_4=6-deoxy-1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl	2059	140 μM	192 μM	77.0 μM
R_1=Ac; R_2=Ph; R_3=H; R_4=6-deoxy-1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl	2060	196 μM	481 μM	76.3 μM
R_1=Ac; R_2=cyclohexyl; R_3=H; R_4=6-deoxy-1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl	2064	19.4 μM	238 μM	14.5 μM
R_1=Ac; R_2=$CH_2CH_2OSO_3Na$; R_3=H; R_4=6-deoxy-1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl	2065	84.7 μM	241 μM	133 μM
R_1=$COCH_2Ph$(*m*-Cl); R_2=H; R_3=H; R_4=6-deoxy-1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl	2066	37.4 μM	433 μM	45.3 μM
R_1=Et; R_2=$CO(CH_2)_2COONa$; R_3=H; R_4=6-deoxy-1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl	2068	338 μM	291 μM	207 μM
R_1=Et; R_2=$CO(CH_2)_4COONa$; R_3=H; R_4=6-deoxy-1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl	2069	160 μM	477 μM	104 μM
R_1=Et; R_2=$CO(CH_2)_9OSO_3Na$; R_3=H; R_4=6-deoxy-1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl	2070	98.6 μM	374 μM	135 μM
R_1=Et; R_2=$CO(CH_2)_4COONa$; R_3=H; R_4=6-deoxy-1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl, mixture of mono- and di- sulfates	2071	72.1 μM	2.24 mM	161 μM
R_1=Ac; R_2=cyclohexyl; R_3=H; R_4=6-deoxy-1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl, mixture of mono- and di-sulfates	2072	37.0 μM	2.98 mM	53.9 μM
R_1=Ac; R_2=Ph; R_3=H; R_4=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-ethyl	2073	97.4 μM	236 μM	402 μM
R_1=Ac; R_2=$(CH_2)_2Ph$; R_3=H; R_4=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-ethyl	2074	11.8 μM	113 μM	28.8 μM
R_1= $COCH_2Ph$(*m*-Cl);; R_2,R_3=H; R_4=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-ethyl	2075	171 μM	837 μM	90.8 μM
R_1=Et; R_2=$CO(CH_2)_2CO_2Na$; R_3=H; R_4=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-ethyl	2076	43.4 μM	118 μM	40.3 μM
R_1=Et; R_2=$CO(CH_2)_4CO_2Na$; R_3=H; R_4=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-ethyl	2077	43.6 μM	188 μM	81.1 μM

	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_1=Et; R_2=$CO(CH_2)_9OSO_3Na$; R_3=H; R_4=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-ethyl	2078	20.0 μM		49.6 μM
R_1=Ac; R_2=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl-)-ethyl; R_3=H; R_4=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-ethy	2009	428 μM		
R_1=1,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-2-yl-acetyl; R_2=Bn; R_3=H; R_4=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-ethyl	2014	5.09 μM	85.1 μM	8.82 μM
R_1=1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl-acetyl; R_2=Bn; R_3=H; R_4=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-ethyl	2034	37.6 μM	16.5 μM	115 μM
R_1=Et; R_2=Bz; R_3=H; R_4=methyl 6-deoxy-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl	2081		480 μM	
R_1=Et; R_2=$CO(CH_2)_2Ph$; R_3=H; R_4=methyl 6-deoxy- 2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl	2082		420 μM	
R_1=Et; R_2=$CO(CH_2)_3Ph$; R_3=H; R_4=methyl 6-deoxy-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl	2083		403 μM	
R_1=Et; R_2=$COCH_2OSO_3Na$; R_3=H; R_4=methyl 6-deoxy - 2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl	2084		192 μM	

Table 4



	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_1=$COCH_2C(CH_3)_2CH_2CO$; R_2=3-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-propyl	2015	2.94 μM	7.56 μM	267 nM
R_1=1,4-*trans*-cyclohexyl; R_2=1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl-acetyl	2016	32.6 μM	81.8 μM	931 nM
R_1=$COCH_2C(CH_3)_2CH_2CO$; R_2=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-ethyl, undersulfated	2057	18.8 μM	61.6 μM	55.6 μM
R_1=$COCH_2C(CH_3)_2CH_2CO$; R_2=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-ethyl	2062	10.3 μM	29.7 μM	17.3 μM

The results presented in Tables 1 to 4 demonstrate that the broad range of compounds embraced by the invention have strong affinity for GAG-binding growth factors and may thus serve as modulators of their activity.

The foregoing embodiments are illustrative only of the principles of the invention, and various modifications and changes will readily occur to those skilled in the art. The invention is capable of being practiced and carried out in various ways and in other embodiments. It is also to be understood that the terminology employed herein is for the purpose of description and should not be regarded as limiting.

The term "comprise" and variants of the term such as "comprises" or "comprising" are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

Any reference to publications cited in this specification is not an admission that the disclosures constitute common general knowledge in Australia.

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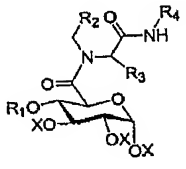
Progen Industries Limited

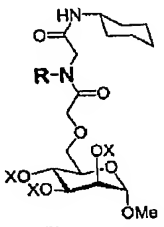
By the patent attorneys for the applicant

CULLEN & CO.

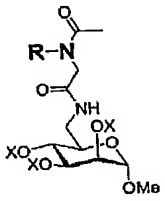
Date: 23 December 2003



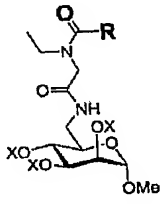
R_1	R_2	R_3	R_4
H	Ph	H	cyclohexyl
SO_3Na	Ph	H	cyclohexyl
SO_3Na	Ph	Ph	cyclohexyl
SO_3Na	Ph	H	Ph
SO_3Na	CH_2OSO_3Na	H	cyclohexyl



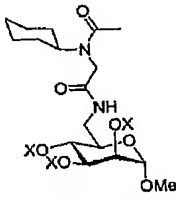
R = Ph
R = CH_2OSO_3Na



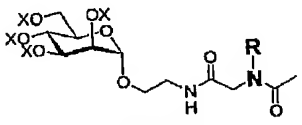
Ph
CH_2Ph
$(CH_2)_2Ph$
Cyclohexyl
PhCl
$(CH_2)_2OX$



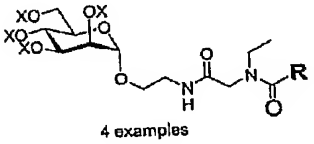
Ph
CH_2PhCl
$(CH_2)_2Ph$
$(CH_2)_3Ph$
$(CH_2)_2CO_2Na$
$(CH_2)_4CO_2Na$
$(CH_2)_9OX$
CH_2OX
$(CH_2)_3OX$



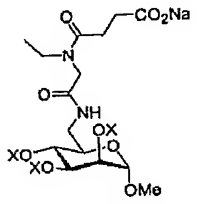
4-OS & 2,3-di-OS
(2:1)



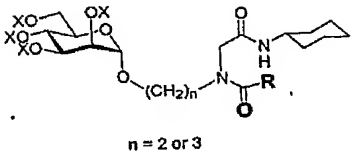
4 examples



4 examples



4-OS & 2,3-di-OS
(2:1)



n = 2 or 3

a. R = CH_2Ph
b. R = $(CH_2)_2Ph$
c. R = $(CH_2)_3Ph$

Fig. 1

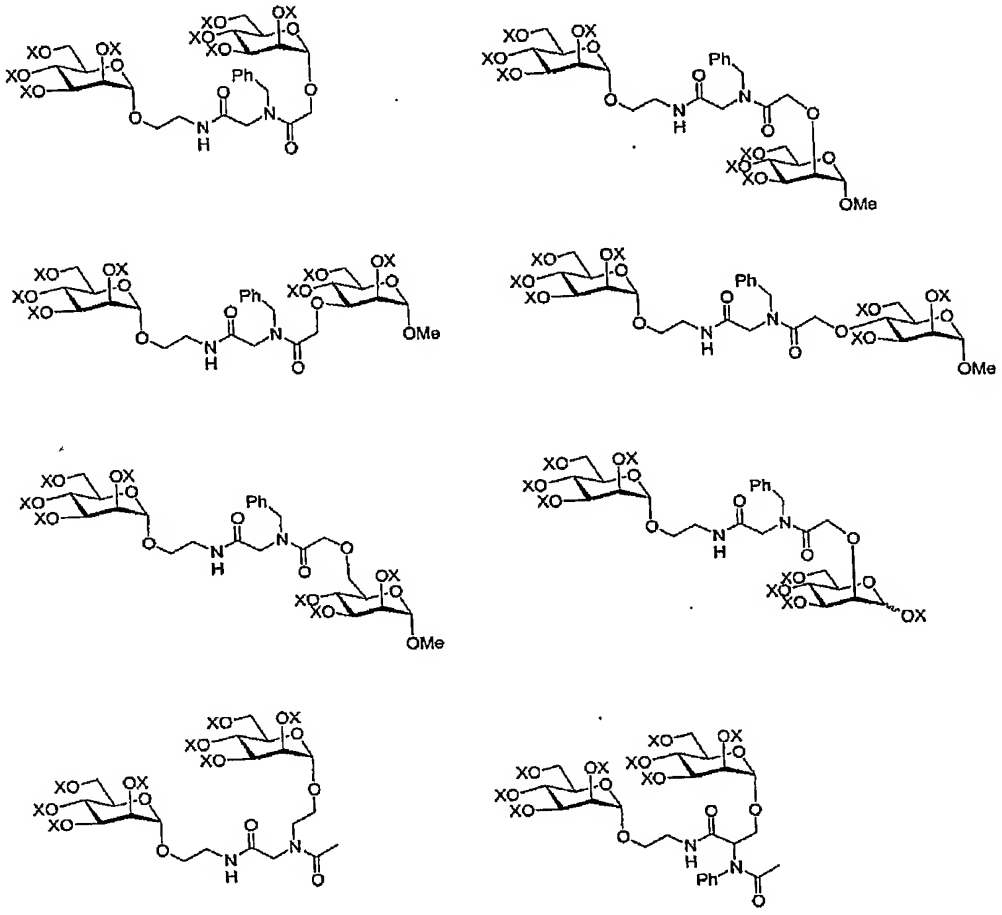


Fig. 2

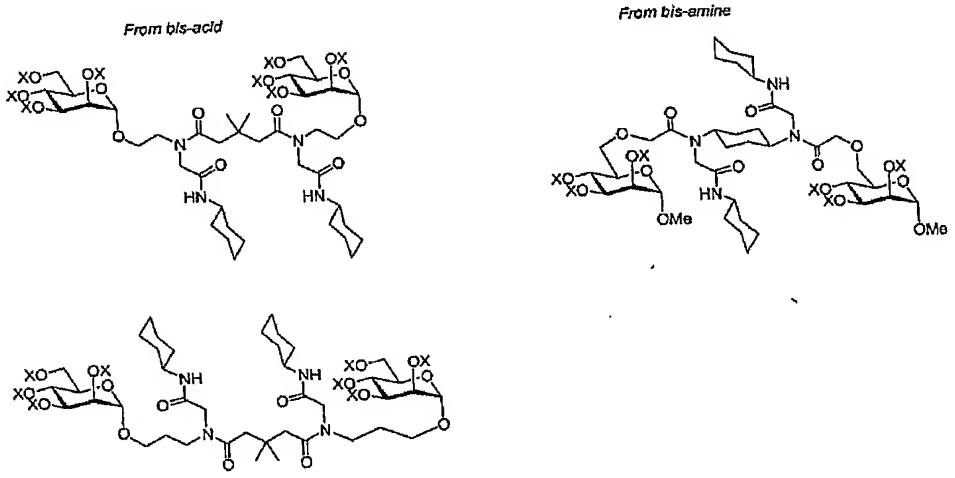

From bis-acid
From bis-amine

Fig. 3

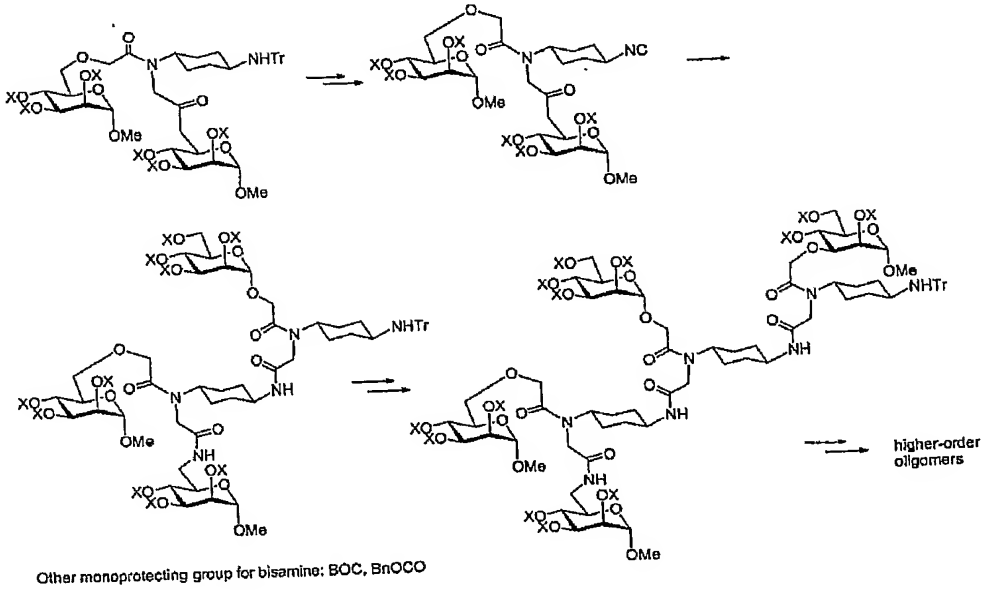
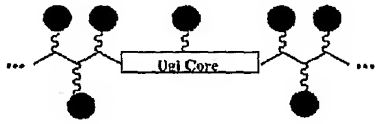
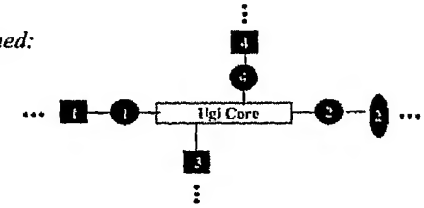

higher-order oligomers
Other monoprotecting group for bisamine: BOC, BnOCO

Fig. 4

Linear:



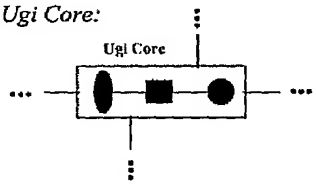
Branched:



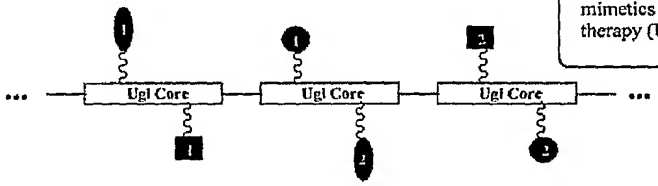
Points of interest:

Comprising charged cyclics or other functional groups (anchors)

Imbedded Ugi Core:



Polymer type sequential assembly (controllable):



This approach has been applied extensively for oligonucleotides mimetics in the area of antisense therapy (US 6355726, 2002).

Fig. 5